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(54) Title: PHOSPHORUS CONTAINING COMPOUNDS AS INHIBITORS OF RETROVIRUSES

(57) Abstract

The present invention relates to peptides of formula (I): $X_1$-$C_8$-$D_9$-$E_{10}$-$F_{11}$-$G_{12}$-Z, having at least one O-phosphate monoester or diester, and parent compounds thereof, which are useful for inhibiting a retrovirus in a mammalian cell infected with said retrovirus.

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# PHOSPHORUS CONTAINING COMPOUNDS AS INHIBITORS OF RETROVIRUSES

## FIELD OF THE INVENTION

The present invention relates to compounds useful for inhibiting a retrovirus in a human cell infected with said retrovirus. More particularly, the present invention provides peptides, having at least one O-phosphate monoester or diester, and certain parent peptides thereof.

## BACKGROUND OF THE INVENTION

An estimated one to one and one-half million people in the United States are infected with a human retrovirus, the human immunodeficiency virus type I, HIV-1, which is the etiological agent of acquired immunodeficiency syndrome, AIDS (C. Norman, Science, 661-662 (1986)). Of those infected, an estimated two hundred and fifty thousands people will develop AIDS in the next five years (J.W. Curran, et al., Science, 1352-1357 (1985)). On March 20, 1987, the FDA approved the use of the compound, zidovudine (AZT), to treat AIDS patients with a recent initial episode of pneumocystis carinii pneumonia, AIDS patients with conditions other than pneumocystis carinii pneumonia or patients infected with the virus with an absolute CD4 lymphocyte count of less than 200/mm$^3$ in the peripheral blood. AZT is a known inhibitor of viral reverse transcriptase, an enzyme necessary for human immunodeficiency virus replication.

U.S. Patent 4,724,232 claims a method of treating humans having acquired immunodeficiency syndrome utilizing 3'-azido-3'-deoxy-thymidine (azidothymidine, AZT).

Since the first description of the malady in the early part of this decade, acquired immunodeficiency disease syndrome (AIDS) and its devastating consequences have been subjects of continuous and intense coverage in both the lay and scientific press. Indeed, a recent edition of Scientific American was entirely devoted to AIDS (Scientific American 289, #4 (1988)), and the literature on the disease and the virus is already so vast as to defy thorough citation. At present, 3'-azido-3'-deoxythymidine (AZT), an inhibitor of the viral reverse transcriptase (RT), remains the therapy of choice, despite its highly toxic side effects.

Human immunodeficiency virus (HIV) has long been recognized as the causative agent in AIDS, although a minority opinion to the contrary has been expressed (e.g., P. Duesberg, Proc. Natl. Acad. Sci., USA, 86:755-764 (1989)). Sequence analysis of the complete genomes from several infective and non-infective HIV-isolates has shed considerable light on the make-up of the virus and the types of molecules that are essential for its replication and maturation to an infective species (L. Ratner, et al., Nature, 313:277-284 (1985)). HIV exhibits the same gag/pol/env organization seen in other retroviruses (L. Ratner, et al., Nature, 313:277-284 (1985)); S. Wain-Hobson, et al., Cell, 40:9-17 (1985); R. Sanchez-Pescador, et al., Science, 227:484-492 (1985); and M.A. Muesing, et al., Nature, 313: 450-458 (1985)).

Reverse transcriptase (RT) is an enzyme unique to retroviruses that catalyzes the

conversion of viral RNA into double stranded DNA. Blockage at any point during the transcription process, by AZT or any other aberrant deoxynucleoside triphosphate incapable of elongation, should have dramatic consequences relative to viral replication. Much work on the RT target is in progress based, in large measure, upon the fact that nucleosides like AZT are easily delivered to cells. However, the inefficiency of phosphorylation steps to the triphosphate, and the lack of specificity and consequent toxicity, constitute major drawbacks to use of AZT and similar nucleosides having a blocked, or missing, 3'hydroxyl group.

The T4 cell receptor for HIV, the so-called CD4 molecule, has also been targeted as an intervention point in AIDS therapy ( R.A. Fisher, et al., Nature, 331:76-78 (1988); R.E. Hussey, et al., Nature, 331:78-81 (1988); and K.C. Deen, et al., Nature, 331:82-84 (1988)). The exterior portion of this transmembrane protein, a molecule of 371 amino acids (sCD4) has been expressed in Chinese hamster ovary (CHO) cells and Genentech ( D.H. Smith, et al., Science, 238:1704-1707 (1987)) has had a product in clinical trials since the fall of 1987. Thus far, little information on efficacy is available beyond the fact that the recombinant sCD4 appears to be relatively non-toxic. The idea behind CD4 based therapy is that the molecules can neutralize HIV by interfering with viral attachment to T4, and other cells which express CD4 on their surfaces. A variant on this theme is to attach cell toxins to CD4 for specific binding and delivery to infected cells which display glycoprotein gp-120 on their surfaces ( M.A. Till, et al., Science, 242:1166-1168 (1988); and V.K. Chaudhary, et al., Nature, 335:369-372 (1988)).

Another therapeutic target in AIDS involves inhibition of the viral protease (or proteinase) that is essential for processing HIV-fusion polypeptide precursors. In HIV and several other retroviruses, the proteolytic maturation of the gag and gag/pol fusion polypeptides (a process indispensable for generation of infective viral particles) has been shown to be mediated by a protease that is, itself, encoded by the pol region of the viral genome (Y. Yoshinaka, et al., Proc. Natl. Acad. Sci. USA, 82:1618-1622 (1985); Y. Yoshinaka, et al., J. Virol., 55:870-873 (1985); Y. Yoshinaka, et al., J. Virol., 57:826-832 (1986); and K. von der Helm, Proc. Natl. Acad. Sci., USA, 74:911-915 (1977)).

The protease (or proteinase), consisting of only 99 amino acids, is among the smallest enzymes known, and its demonstrated homology to aspartyl proteases such as pepsin and renin ( L.H. Pearl and W.R. Taylor, Nature, 329: 351-354 (1987); and I. Katoh, et al., Nature, 329:654-656 (1987)), led to inferences regarding the three-dimensional structure and mechanism of the enzyme (L.H. Pearl and W.R. Taylor, Nature, 329:351-354 (1987)) that have since been borne out experimentally. Active HIV protease has been expressed in bacteria (see, e.g., P.L. Darke, et al., J. Biol. Chem., 264:2307-2312 (1989)) and chemically synthesized ( J. Schneider and S.B. Kent, Cell, 54:363-368 (1988); and R.F. Nutt, et al., Proc. Natl.

Acad. Sci., USA, 85:7129-7133 (1988)). Site directed mutagenesis (P.L. Darke, et al., J. Biol. Chem., 264: 2307-2312 (1989); and N.E. Kohl, et al., Proc. Natl. Acad. Sci., USA, 85:4686-4690 (1988) and pepstatin inhibition (P.L. Darke, et al., J. Biol. Chem., 264:2307-2312 (1989); S. Seelmeier, et al., Proc. Natl. Acad. Sci., USA, 85:6612-6616 (1988); C.-Z. Giam and I. Borsos, J. Biol. Chem., 263:14617-14720 (1988); and J. Hansen, et al., EMBO J., 7:1785-1791 (1988)) have provided evidence for HIV protease's mechanistic function as an aspartyl protease. A recent study has demonstrated that the protease cleaves at the sites expected in peptides modeled after the regions actually cleaved by the enzyme in the gag and pol precursor proteins during viral maturation (P.L. Darke, et al., Biochem. Biophys. Res. Communs., 156:297-303 (1988)). X-ray crystallographic analysis of the HIV-protease (M.A. Navia, et al., Nature, 337:615-620 (1989)) and a related retroviral enzyme from Rous sarcoma virus (M. Miller, et al., Nature, 337:576-579 (1989)) reveal an active site in the protease dimer that is identical to that seen in other aspartyl proteases, thus supporting the supposition (L.H. Pearl and W.R. Taylor, Nature, 329:351-354 (1987)) that the HIV enzyme is active as a dimer.

To date, the scientific search for a fully effective and safe means of inhibiting retroviruses in a human hosting such a virus, and thereby effectively treating diseases caused by such a virus, such as acquired immunodeficiency syndrome (AIDS), continues.

J. Moss and H. Bundgaard, International Journal of Pharmaceutics, 66 (1990) 39-45, discloses the transdermal delivery of thyrotropin-releasing hormone (TRH) via the prodrug-N-octyloxycarbonyl derivative.

J. Moss, A. Buur and H. Bundgaard, International Journal of Pharmaceutics, 66 (1990) 183-191, discloses that the prodrug N-alkoxycarbonyl derivatives of thyrotropin-releasing hormone (TRH) did not improve the oral bioavailability of TRH due to the greater susceptibility of the prodrugs to undergo enzymatic degradation.

International publication WO 90/07520, published 12 July 1990, discloses oxysteryle phosphates having anti-cancer and immunodepressant properties.

International publication, WO 90/08550, published 9 August 1990, discloses antivirals and methods for increasing the antiviral activity of AZT by administering AZT in combination with certain purine compounds or their prodrugs. Such prodrugs include 5-amino-3'-(2-methyl-1-propoxycarbonyl)-1-β-D-ribofuranosyl-imidazole-4-carboxamide; 5-amino-3'-(1-propoxycarbonyl) 1-β-D-ribofuyranosyl-imidazole-4-carboxamide, and 2', 3'-cyclocarbonate AICA riboside.

European published application 0 214 009 discloses enaminones as prodrugs of primary and secondary amines.

U.S. Patent 4,650,803 discloses water soluble prodrugs of rapamycin such as the glycinate, propionate and pyrrolidine butyrate prodrugs.

European published application 0 365 956 A2 discloses therapeutic compositions of amino-oxodihydroisoindolo-quinazoline which contain the radical of an amino acid, a dipeptide or a tripeptide which show enhanced solubility in water.

U.S. Patent 4,163,058 and 4,260,769 disclose 5,5-diphenyl-hydantoins containing a phosphate group which offer enhanced solubility.

U.S. Patent Application 7-258 417, published in Derwent Abstract 51,003-990 discloses phosphorothioate oligodeoxyribonucleotide analogs which are useful for inhibiting replication of viruses and retroviruses. Phosphorothioates are compounds in which one of the non-bridging oxygen atoms in the phosphate portion of the nucleotide is replaced by sulfur.

Antimicrobial Patent Fast-Alert, week ending 4 January 1991, discloses an in vitro hydrolyzable pro-drug combination of Methampicillin and the β-lactamace inhibitor Sulbactam which has therapeutic utility in the treatment of bacterial infections.

Derwent Abstract, Accession Number 89-287098/40, discloses nerve growth factor peptides which may contain a phosphate group.

European published application 0 354 108 discloses new O-sulphated or phosphorylated tyrosine analogues for treating central nervous system diseases.

U.S. Patent 4,954,616 discloses the use of guanidine-related compounds, having a protecting group, such as triphenylphosphonoethyloxycarbonyl, in solution-phase peptide synthesis.

U.S. Patent 4,775,743 discloses peptide derivatives of the general formula (Hydrophobic radical)-Pro-Hyp-(Hydrophilic radical) wherein Hyp is hydroxy-prolyl and wherein an example of a hydrophilic radical is phosphate. These peptides are described as being useful as an anti-agglutination agent.

U.S. Patent 4,952,493 discloses a method for preparing selected peptide substrates for detecting the activity of virus-specified proteases. Specific tetrapeptide substrates are disclosed which are conjugates of protease-cleavable indicator groups and peptide sequences resembling picornavirus protease cleavage recognition sites.

U.S. Patent 4,716,222 describes chromogenic substrates, such as 2H-7-0-(Phosphoryl)-4-methyl-8-nitrobenzopyran-2-one,which are useful for the detection and determination of hydrolases, such as acid phosphatase.

U.S. Patent 4,617,377 discloses new synergistine derivatives which may be substituted with a dialkylphosphoryloxy radical, which are useful as intermediates.

International Publication WO 89/10960 and WO 89/10961, published 16 November 1989, phosphorus-containing haptens and immunogens, comprising a phosphorus-containing hapten and a carrier molecule, which are useful for producing antibodies to catalyze the cleavage or formation of amide, ester or glycosidic bonds. It also discloses a method for

treating acquired immune deficiency syndrome by inhibiting human immunodeficiency virus by treatment with a catalytic antibody elicited with a hapten or immunogen.

Patent Fast-Alert, week ending 22 February 1991, discloses phosphorylated glycosidase inhibitor prodrugs of desoxynojirimycin, which exhibit glycosidase inhibitory activity. They are useful in the treatment of gastrointestinal problems.

U.S. Patent 4,407,794 describes peptides which are useful as analgesic and psychotropic agents which may have a phosphatidylethanolamine chain at the C-terminus.

INFORMATION DISCLOSURE

Chemical Abstract, Accession Number 84-027490/05, discloses spergualin 15-phosphate which is useful as a carcinostatic.

European published application 0 338 372 discloses the N-phosphorylation of basic nitrogenous drug compounds to produce pro-drugs with enhanced water solubility or lipid solubility or reduced toxicity. The compounds of the present invention are O-phosphorylated. Furthermore, no where does this reference teach or suggest the peptidic compounds of the present invention.

U.S. Patent 4,663,310 discloses renin inhibitors containing 2-substituted statine and which may have a phosphate-substituted phenyl group at the C-terminus.

U.S. Patents 4,298,523 and 4,369,137 disclose solution phase methods, intermediates, and compositions for preparing useful peptides wherein a phosphate group is used as an amino-protecting group.

U.S. Patent 4,661,473 discloses renin inhibitory peptides which may have a phosphate group at the C-terminus or in the peptide chain as part of a modified amino acid residue.

U.S. Patent 4,661,472 discloses peptides which may be useful to treat steroid-dependent tumors.

A.A. Sinkula and S.H. Yalkowsky, J. of Pharm. Sci., Vol. 64, No.2, Feb. 1975, discloses phosphamide as a prodrug linkage to increase the absorption of the active drug.

The Peptides by E. Schröder and K. Lübke, Vol. 1, Methods of Peptide Synthesis (1965), describes the preparation of O-phosphoryl-amino acids of peptides.

In R.H. Hook, C.J. Eastwood and G.J. Wright, Drug Metabolism Review 4 (2), 249-265 (1975), showed that the phosphate ester of oxyphenbutazone is an effective prodrug capable of enhancing the plasma concentration of oxyphenbutazone in dogs.

CLEOCIN PHOSPHATE® Sterile Solution and CLEOCIN T® Topical Gel, Topical Lotion and Topical Solution, which are useful as antibiotics, contain clindamycin phosphate, which is a water soluble ester of clindamycin and phosphoric acid. It is biologically inactive and rapidly converted to active clindamycin. These drugs are currently manufactured and marketed by The Upjohn Company. See R.M. DeHaan, C.M. Metzler. D. Schellenberg and

W.D. Vandenboech, J. Clin. Pharmacol. 13, 190 (1973).

J.W. Perich and R.B. Johns, Aust. J. Chem., 1990, 43, 1603-8, 1623-32, and 1633-42, describes the unexpected dephosphorylative rearrangement of the simple phosphopeptides Ac-Ser($PO_3Bzl_2$)-NHMe and Ac-Ser-($PO_3H_2$)-NHMe; describes the phosphorotriester and "phosphite-triester" phosphorylation of protected serine-containing peptides; describes the global "phosphite-triester" phosphorylation of protected serine derivatives and peptides by using dibenzyl or di-t-butyl N,N-diethylphosphoramidite; and describes the global "phosphite-triester" phosphorylation of multiple-serine-containing peptides by using dibenzyl N,N-diethyl-phosphoramidite.

The following patent applications disclose peptides that are useful as renin inhibitors and HIV protease inhibitors which contain a $(HO)_2P(O)O-(CH_2)_n-C(O)-$ group at the N-terminus: PCT International Publication Number WO 90/12804, published 1 November 1990.

European published applications 0 337 714 and 0 356 223 disclose HIV protease inhibitors which do not have an amino acid analog at the D-9 position in front of the transition state insert. These peptides may have phosphate-substituted aryl and Het groups in their transition state inserts, in the amino acid moieties occurring after their transition state inserts and at their C-terminus. They may also have phosphate-substituted alkyl and carbocyclic groups at their C-terminus. These applications also disclose peptides having a phosphate group in their peptide chain as part of a modified amino acid residue at their N-terminus and in their transition state inserts. However, no where do these applications disclose the phosphate groups of the present invention.

T.A. Lyle, et al., J. Med. Chem., 34:1228-1230 (1991), discloses benzocycloalkyl amines, including aminohydroxyindane, as C-termini for HIV protease inhibitors.

V.J. Stella, W.N.A. Charman and V.H. Naringrekar, Drugs 29:445-473 (1985), discloses that a prodrug is used to improve the aqueous solubility to allow intravenous administration of a drug. It also discloses phosphate prodrug.

European Patent Application 0 346 847 discloses amino acid derivatives having an optionally substituted trimethylene or tetramethylene groups or which carries a fused cycloalkane, aromatic or heteroaromatic ring at the C-terminus.

Chemical Abstracts 113:172751p discloses the preparation of peptide analogs, such as 2,5,8,11-tetraoxa-14,20-diazapentacosan-25-amide, 18,24-di-2-butenyl-N-butyl-15,21-bis-(cyclohexylmethyl)-22-hydroxy-16,19-dioxo-13-thioxo [Reg. No. 129525-29-7], as renin inhibitors. J. of Protein Chemistry, Vol. 10, No. 5, 1991, pages 553-563, discusses the characterization of recombinant human renin and discloses a renin inhibitor peptide A-65317 with an N-terminus ether moiety. Besides having different utilities, these compounds are structurally far different from the compounds of the present invention, which may have an

ether-containing moiety at the N-terminus.

Chemical Abstracts, Accession Number 91-227903/31, discloses peptides having a modified polyethylene glycol moiety at the N-terminus, for example, calcitonin GRP and elastase, which have prolonged activity.

In Peptide Research, Vol. 4, No. 6 (1991), pages 334-339, d-gluconic acid and α-carboxymethyl polyethylene-glycol-w-methyl ether (PEG) were covalently bound at $N^{\alpha}$-amino group of H-Phe-Arg-pNa for study purposes.

The following references disclose the chemistry and biochemistry of biotin: J. -P. Bonjour, "Biotin" in The Handbook of Vitamins, 2nd Ed. 1991 (Ed. L. J. Machlin, Marcel Dekker/New York, pp. 393-427; Said, H. M. Biochem. J. 1991, 279, 671-674.

The following published patent applications and patents disclose non-phosphate peptides that are useful as renin inhibitors: European published application 0 173 481 and U.S. Patent 4,880,781; U.S. Patent 4,864,017 (having diol transition state inserts); European published application 0 364 493, published 25 April 1990, (having aryl acid derived moieties at the N-terminus); and European published application 0 397 779, published 22 November 1990, (having N-terminal polar end groups).

PCT International Publication Number WO 91/06561, published 16 May 1991, discloses a method for treating HIV and other retroviruses and non-phosphate peptides useful therefor.

## SUMMARY OF THE INVENTION

The present invention particularly provides:

A compound of the formula I

$$X_1\text{-}C_8\text{-}D_9\text{-}E_{10}\text{-}F_{11}\text{-}G_{12}\text{-}Z$$

wherein $X_1$ is

a) hydrogen,

b) $C_1$-$C_7$ alkyl,

c) $-(CH_2)_p$-aryl,

d) $-(CH_2)_p$-Het,

e) $-(CH_2)_p$-$C_3$-$C_7$cycloalkyl,

f) $R_5$-O-$(CH_2)_q$-C(O)-,

g) $R_5$-$CH_2$-O-C(O)-,

h) $R_5$-O-C(O)-,

i) $R_5$-$(CH_2)_n$-C(O)-,

j) $R_5$-$(CH_2)_n$-C(S)-,

k) $R_4N(R_4)$-$(CH_2)_n$-C(O)-,

l) $R_5$-$SO_2$-$(CH_2)_q$-C(O)-,

m) $R_5$-$SO_2$-$(CH_2)_q$-O-C(O)-,

n) $R_5$-$(CH_2)_n$-$SO_2$,

o) Z-C(O)-CH(OH)-$CH(CH_2R_1)$-C(O)-

p) $R_5$-$(CH_2)_p$ CH=CH-$(CH_2)_p$-C(O)-,

q) $R_5(CH_2)p$ CH=CH-$(CH_2)_p$-O-C(O),

r) $R_{27}(CH_2)_q$-C(O)-,

s) $(OH)_2(O)PO$-aryl-$(CH_2)_p$-C(O)-,

t) $(OH)_2(O)PO$-Het-$(CH_2)_p$-C(O)-,

u) aryl-$(W_1)_j$-$(CH_2)_m$-$W_1$-aryl-C(O)-,

v) aryl-$W_1$-$(CH_2)_m$-$W_1$-$(CH_2)_m$-C(O)-,

w) Het-$(CH_2)_m$-$W_1$-aryl-C(O)-,

x) $C_1$-$C_6$ alkyl-CH(OH)-C(O)-,

y) biotinoyl,

z) biotinoyl-NH-$(CH_2)_q$-C(O)-, or

a1) 2-((4-([3aS-(3aα,4β-6aα)]-1H-thieno-[3,4-d]imidazole-2(3H)-on-4yl)-pent-1-yl)-$W_1$-aryl-C(O)-;

wherein $C_8$ is absent or a divalent moiety of the formula $XL_1$, $XL_2$, $XL_{2a}$, $XL_{2b}$ or other amino acyl derivative;

wherein $D_9$ is Pro, absent or a divalent moiety of the formula $XL_3$, $XL_{2a}$, $XL_{2b}$ or other amino acyl derivative;

wherein $E_{10}$-$F_{11}$ is a divalent moiety of the formula $XL_6$, $XL_{6b}$, $XL_{6c}$, $XL_{6d}$, $XL_{6e}$, II, III, IV, $XL_{6p}$, $XL_{6cp}$, $XL_{6ep}$, $XL_{6ccp}$, $II_{cp}$, V, Vp, VI or VII;

wherein $G_{12}$ is absent or a divalent moiety of the formula $XL_4$, $XL_{4a}$ or other amino acyl derivative;

wherein Z is

a) -O-$R_{10}$,

b) -N($R_4$)$R_{14}$,

c) $C_4$-$C_8$cyclic amino,

d) -NH$R_{120}$,

e) -NH-$(CH_2)_r$ pyridine (N-oxide),

f) Het bonded via a nitrogen atom,

g) -NH$(CH_2)_q$NH-Het,

h) 1-amino indanyl optionally substituted at the 2- or 3- position by one or two hydroxy or -OC(O)$CH_3$,

i) 1-amino-2,3-cyclicmonophosphate indanyl, or

j) -NH-$(CH_2)_q$-CH=CH-$(CH_2)_q$-NH-Het;

wherein R is

a) $-(CH_2)_n$-isopropyl,

b) $-(CH_2)_n$-isobutyl,

c) $-(CH_2)_n$-phenyl, or

d) $-(CH_2)_n-C_3-C_7$cycloalkyl;

wherein $R_1$ is

a) hydrogen,

b) $C_1-C_5$alkyl,

c) aryl,

d) $C_3-C_7$cycloalkyl,

e) -Het,

f) $C_1-C_3$alkoxy, or

g) $C_1-C_3$alkylthio;

wherein $R_2$ is

a) hydrogen, or

b) $-CH(R_3)R_4$;

wherein $R_3$ is

a) hydrogen,

b) hydroxy,

c) $C_1-C_5$alkyl,

d) $C_3-C_7$cycloalkyl,

e) aryl,

f) -Het,

g) $C_1-C_3$alkoxy,

h) $C_1-C_3$alkylthio, or

i) $-OP(O)(OH)_2$;

wherein $R_4$ at each occurrence is the same or different as is

a) hydrogen,

b) $C_1-C_5$alkyl,

c) $-(CH_2)_p$-aryl,

d) $-(CH_2)_p$-Het,

e) $-(CH_2)_p-C_3-C_7$cycloalkyl, or

f) 1- or 2-adamantyl;

wherein $R_5$ is

a) $C_1-C_6$alkyl,

b) $C_3-C_7$cycloalkyl,

c) aryl,

d) -Het,

e) 5-oxo-2-pyrrolidinyl,

f) 1 or 2-adamantyl,

g) -aryl-$OP(O)(OH)_2$, or

h) -Het-$OP(O)(OH)_2$;

wherein $R_6$ is

a) hydrogen,

b) $C_1$-$C_5$alkyl,

c) -$(CH_2)_p$-aryl,

d) -$(CH_2)_p$-Het,

e) -$(CH_2)_p$-$C_3$-$C_7$cycloalkyl,

f) 1- or 2-adamantyl,

g) -$(CH_2)_p$-aryl-$OP(O)(OH)_2$,

h) -$(CH_2)_p$-Het-$OP(O)(OH)_2$, or

i) -$(CH_2)_p$-$OP(O)(OH)_2$;

wherein $R_7$ is

a) hydrogen,

b) $C_1$-$C_5$alkyl,

c) -$(CH_2)_n$-hydroxy,

d) amino $C_1$-$C_4$alkyl-,

e) guanidinyl $C_1$-$C_3$alkyl-,

f) aryl,

g) -Het,

h) methylthio,

i) -$(CH_2)_p$-$C_3$-$C_7$cycloalkyl,

j) amino,

k) -$(CH_2)_n$-COOH,

l) -$(CH_2)_n$-$COOC_1$-$C_6$ alkyl,

m) -$(CH_2)_n$-$CONR_{22}R_{26}$,

n) -$(CH_2)_n$-$OP(O)(OH)_2$,

o) -aryl-$OP(O)(OH)_2$, or

p) -Het-$OP(O)(OH)_2$;

wherein $R_8$ is

a) hydrogen

b) $C_1$-$C_5$alkyl,

c) hydroxy,

d) aryl,

e) -Het,

f) guanidinyl $C_1$-$C_3$alkyl-,

g) -$(CH_2)_p$-$C_3$-$C_7$cycloalkyl, or

h) -$OP(O)(OH)_2$;

wherein $R_{10}$ is

a) hydrogen,

b) $C_1$-$C_5$alkyl,

c) -$(CH_2)_n R_{16}$,

d) -$(CH_2)_n R_{17}$,

e) $C_3$-$C_7$cycloalkyl,

f) a pharmaceutically acceptable cation,

g) -$CH(R_{25})$-$CH_2$-$R_{15}$, or

h) -$CH_2$-$CH(R_{12})$-$R_{15}$;

wherein $R_{11}$ is -R or -$R_2$;

wherein $R_{12}$ is -$(CH_2)_n$-$R_{13}$;

wherein $R_{13}$ is

a) aryl,

b) amino,

c) mono-, di- or tri-$C_1$-$C_3$alkylamino,

d) -Het,

e) $C_1$-$C_5$alkyl,

f) $C_3$-$C_7$cycloalkyl,

g) $C_2$-$C_5$alkenyl,

h) $C_3$-$C_7$cycloalkenyl,

i) hydroxy,

j) $C_1$-$C_3$alkoxy,

k) $C_1$-$C_3$alkanoyloxy,

l) mercapto,

m) $C_1$-$C_3$alkylthio,

n) -COOH,

o) -CO-O-$C_1$-$C_6$alkyl,

p) -CO-O-$CH_2$-($C_1$-$C_3$alkyl)-N($C_1$-$C_3$alkyl)$_2$,

q) -CO-$NR_{22}R_{26}$;

r) $C_4$-$C_7$cyclic amino,

s) $C_4$-$C_7$cycloalkylamino,

t) guanidyl,

u) cyano,

v) N-cyanoguanidyl,

w) cyanoamino,

x) (hydroxy $C_2$-$C_4$alkyl)amino, or

y) di-(hydroxy$C_2$-$C_4$alkyl)amino;

wherein $R_{14}$ is

a) hydrogen,

b) $C_1$-$C_{10}$alkyl,

c) -$(CH_2)_n$-$R_{18}$,

d) -$(CH_2)_n$-$R_{19}$,

e) -$CH(R_{25})$-$CH_2$-$R_{15}$,

f) -$(CH_2)_q$-$CH(R_{12})$-$R_{15}$,

g) (hydroxy $C_1$-$C_8$alkyl),

h) hydroxy $C_1$-$C_8$ alkyl-aryl, or

i) ($C_1$-$C_3$ alkoxy) $C_1C_8$ alkyl;

wherein $R_{15}$ is

a) hydroxy,

b) $C_3$-$C_7$cycloalkyl,

c) aryl,

d) amino,

e) mono-, di-, or tri-$C_1$-$C_3$alkylamino,

f) mono- or di-(hydroxy $C_2$-$C_4$alkyl)amino,

g) -Het,

h) $C_1$-$C_3$alkoxy-,

i) $C_1$-$C_3$alkanoyloxy-,

j) mercapto,

k) $C_1$-$C_3$alkylthio-,

l) $C_1$-$C_5$alkyl,

m) $C_4$-$C_7$cyclic amino,

n) $C_4$-$C_7$cycloalkylamino,

o) $C_1$-$C_5$alkenyloxy, or

p) $C_3$-$C_7$cycloalkenyl;

wherein $R_{16}$ is

a) aryl,

b) amino,

c) mono- or di-($C_1$-$C_3$alkyl)amino,

d) hydroxy,

e) $C_3$-$C_7$cycloalkyl,

f) $C_4$-$C_7$cyclic amino, or

g) $C_1$-$C_3$alkanoyloxy;

wherein $R_{17}$ is

a) -Het,

b) $C_1$-$C_5$alkenyl,

c) $C_3$-$C_7$cycloalkenyl,

d) $C_1$-$C_3$alkoxy,

e) mercapto,

f) $C_1$-$C_3$alkylthio,

g) -COOH,

h) -CO-O-$C_1$-$C_6$alkyl,

i) -CO-O-$CH_2$-($C_1$-$C_3$alkyl)-N($C_1$-$C_3$alkyl)$_2$,

j) -CO-$NR_{22}R_{26}$,

k) tri-$C_1$-$C_3$alkylamino,

l) guanidyl,

m) cyano,

n) N-cyanoguanidyl,

o) (hydroxy $C_2$-$C_4$alkyl)amino,

p) di-(hydroxy $C_2$-$C_4$alkyl)amino, or

q) cyanoamino;

wherein $R_{18}$ is

a) amino,

b) mono-, or di-($C_1$-$C_3$alkyl)amino,

c) $C_4$-$C_7$cyclic amino,

d) $C_4$-$C_7$cycloalkylamino, or

e) -$CH(NH_2)(CO_2H)$;

wherein $R_{19}$ is

a) aryl,

b) -Het,

c) tri-$C_1$-$C_3$alkylamino,

d) $C_3$-$C_7$cycloalkyl,

e) $C_2$-$C_5$alkenyl,

f) $C_3$-$C_7$cycloalkenyl,

g) hydroxy,

h) $C_1$-$C_3$alkoxy,

i) $C_1$-$C_3$alkanoyloxy,

j) mercapto,

k) $C_1$-$C_3$alkylthio,

l) -COOH,

m) -CO-O-$C_1$-$C_6$alkyl,

n) -CO-O-$CH_2$-($C_1$-$C_3$alkyl)-N($C_1$-$C_3$alkyl)$_2$,

o) -CO-$NR_{22}R_{26}$,

p) guanidyl,

q) cyano,

r) N-cyanoguanidyl,

s) cyanoamino,

t) (hydroxy $C_2$-$C_4$alkyl)amino,

u) di-(hydroxy $C_2$-$C_4$alkyl)amino, or

v) -$SO_3H$;

wherein $R_{20}$ is

a) hydrogen,

b) $C_1$-$C_5$alkyl, or

c) aryl-$C_1$-$C_5$alkyl;

wherein $R_{22}$ is

a) hydrogen, or

b) $C_1$-$C_3$alkyl;

wherein $R_{23}$ is

a) -$(CH_2)_n$-OH,

b) -$(CH_2)_n$-$NH_2$,

c) aryl,

d) $C_1$-$C_3$alkyl, or

e) -$(CH_2)_n$-OP(O)$(OH)_2$;

wherein $R_{24}$ is

a) -$R_1$,

b) -$(CH_2)_n$-OH,

c) -$(CH_2)_n$-$NH_2$, or

d) -$(CH_2)_n$-OP(O)$(OH)_2$;

wherein $R_{25}$ is

a) $-(CH_2)_n-R_{13}$,

b) hydrogen,

c) $C_1$-$C_3$alkyl, or

d) phenyl-$C_1$-$C_3$alkyl;

wherein $R_{26}$ is

a) hydrogen,

b) $C_1$-$C_3$alkyl, or

c) phenyl-$C_1$-$C_3$alkyl;

wherein $R_{27}$ is

a) -COOH,

b) $-COOC_1$-$C_6$ alkyl,

c) $-CONR_{22}R_{26}$,

d) $-CH(NH_2)COOH$, or

e) hydroxy;

wherein $R_{30}$ and $R_{31}$ together represent a trimethylene or tetramethylene group which is optionally substituted by hydroxy, alkoxycarbonylamino or acylamino or in which one $-CH_2-$ group is replaced by -NH-, -N(alkoxycarbonyl)-, -N(acyl)- or -S- or which carries a fused cycloalkane, aromatic or heteroaromatic ring;

wherein $R_{120}$ is

a) $R_{126}C[(CH_2)_qOR_{121}]_2(CH_2)_q-$,

b) a moiety of Formula XXX,

c) a moiety of Formula XXXI

d) $-CH_2(CHOR_{121})_xCH_2OR_{121}$,

e) $R_{121}OCH_2(CHOR_{121})_yCH-(CHOR_{121})_zCH_2OR_{121}$,

f) a moiety of Formula XXXII, or

g) $R_{121}OCH_2-C(CH_2OR_{121})_2-$;

wherein $R_{121}$ is

a) hydrogen,

b) $C_1$-$C_6$alkyl,

c) $-(CH_2)_n$-aryl, or

d) $-C(O)R_{123}$;

wherein $R_{123}$ is

a) $C_1$-$C_5$ alkyl, or

b) $-(CH_2)_n$-phenyl;

wherein $R_{126}$ is

a) hydrogen, or

b) $(CH_2)_nOR_{121}$;

wherein $R_{128}$ is

a) hydrogen, or

b) $-(CHOR_{121})_tCH_2OR_{121}$;

wherein Q is

a) $CH_2$,

b) $CHOR_{121}$, or

c) C(O);

wherein $W_1$ is

a) -O-, or

b) -S-;

wherein j is zero or one;

wherein m is one to three, inclusive;

wherein for each occurrence n is independently an integer of zero to six, inclusive;

wherein p is zero to two, inclusive;

wherein q is an integer of one to six, inclusive;

wherein r is zero to five, inclusive;

wherein s is an integer of zero or one so that the sum of u plus v plus s is three or four;

wherein t is an integer of zero to three, inclusive;

wherein u is an integer of zero to three, inclusive;

wherein v is an integer of zero to four, inclusive;

wherein w is an integer of two or three;

wherein x is an integer of two to seven, inclusive;

wherein y is an integer of zero to six, inclusive; and

wherein z is an integer of zero to six so that the sum of y plus z does not exceed six;

wherein aryl is phenyl or naphthyl substituted by zero to three of the following:

a) $C_1$-$C_3$alkyl,

b) hydroxy,

c) $C_1$-$C_3$alkoxy,

d) halo,

e) amino,

f) mono- or di-$C_1$-$C_3$alkylamino,

g) -CHO,

h) -COOH,

i) $COOR_{26}$,

j) $CONHR_{26}$,
k) nitro,
l) mercapto,
m) $C_1$-$C_3$alkylthio,
n) $C_1$-$C_3$alkylsulfinyl,
o) $C_1$-$C_3$alkylsulfonyl,
p) -$N(R_4)$-$C_1$-$C_3$alkylsulfinyl,
q) -$SO_3H$,
r) $SO_2NH_2$,
s) -CN,
t) -$CH_2NH_2$,
u) -$O[(CH_2)_2O]_qCH_3$,
v) -$[O-(CH_2)_2]_q$-$OCH_3$,
w) -$[O-(CH_2)_2]_q$-$NR_{22}R_{26}$,
x) -$[O-(CH_2)_2]_q$-Het, or
y) -O-C(O)-$C_1$-$C_3$ alkyl;

wherein -Het is a 5- or 6-membered saturated or unsaturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another heterocycle and the ring may be connected through a carbon or secondary nitrogen in the ring or an exocyclic nitrogen; and if chemically feasible, the nitrogen and sulfur atoms may be in the oxidized forms; and substituted by zero to three of the following:

a) $C_1$-$C_5$alkyl,
b) hydroxy,
c) hydroxy ($C_1$-$C_5$alkyl),
d) halogen,
e) amino,
f) amino ($C_1$-$C_5$alkyl),
g) -CHO,
h) -$CO_2H$,
i) -$CO_2$-($C_1$-$C_5$alkyl),
j) -$CONH_2$,
k) -CONH-($C_1$-$C_5$alkyl),
l) nitro,
m) mercapto,
n) mercapto ($C_1$-$C_5$alkyl),

o) $-SO_3H$,

p) $-SO_2NH_2$,

q) -CN,

r) $-O-C_1-C_5$alkyl, or

s) $-[O-(CH_2)_2]_q-OCH_3$;

and pharmacologically acceptable salts thereof;

with the provisos that:

1) at least one phosphate group must be present; and

2) no more than three phosphate groups are present.

By "amino acyl derivatives" is meant any of the naturally occurring amino acids such as: glycine, alanine, valine, leucine, isoleucine, phenylalanine, lysine, proline, tryptophan, methionine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, arginine, ornithine, and histidine, and synthetic derivatives thereof. These compounds may be in the L or D configuration and are well known and readily available to those skilled in the art. It also includes the phosphate ester of serine, threonine, and tyrosine.

In this invention, phosphate monoesters include the phosphate esters of alkanols and hydroxy-substituted aromatic and heterocyclic moieties. Phosphate diesters include the cyclic phosphate esters derived from dihydroxy alkanes in which the hydroxyl groups are on adjacent carbons (1,2-diols) or on carbons separated by one carbon atom (1,3-diols).

Poor solubility of HIV protease inhibitory peptides/peptidimimetic within patients is a substantial problem. The present invention provides for the O-phosphorylation of compounds to produce pro-drugs with enhanced water solubility, bioavailability, improved absorption, increased duration of action, or reduced toxicity. The pro-drugs are hydrolyzed in the body, regenerating the original (parent) drugs with the release of a salt of phosphoric acid.

Susprisingly and unexpectedly, the parent compounds of the compounds of the present invention are effective and potent inhibitors of HIV protease. They have also been found to inhibit HIV protease in cell cultures, as described below. Therefore, the parent compounds of the compounds of formula I inhibit retroviral proteinases and thus inhibit the replication of the virus. They are useful for treating patients infected with human immunodeficiency virus (HIV) which results in acquired immunodeficiency syndrome (AIDS) and related diseases. The parent compounds have low to moderate renin inhibitory activity but are surprisingly and unexpectedly potent retroviral protease inhibitors.

Thus, both the parent compounds and the pro-drug compounds of the present invention are useful as retroviral protease inhibitors.

Examples of the parent compounds of the present invention include:

A compound of the formula I

$$X_1\text{-}C_8\text{-}D_9\text{-}E_{10}\text{-}F_{11}\text{-}G_{12}\text{-}Z \qquad I$$

wherein $X_1$ is $X_2$-[$(CH_2)_2$-O]$_m$-aryl-O-$(CH_2)_n$-C(O)-;

wherein $X_2$ is

a) $H_3CO$-,

b) $(R_4)_2N$-, or

c) Het;

wherein m is five or six;

wherein n is zero to six, inclusive;

wherein $C_8$ is absent;

wherein $D_9$ is the moiety $XL_3$;

wherein $E_{10}$-$F_{11}$ is the moiety $XL_6$ or II;

wherein $G_{12}$ is absent or is the moiety $XL_4$;

wherein Z is

a) $-N(R_4)_2$, or

b) $-NHX_3$;

wherein $X_3$ is

a) $-(CH_2)_n$-Het,

b) $-(CH_2)_n$-aryl, or

c) 1-amino indanyl optionally substituted at the 2- or 3- position by one or two hydroxy or $-OC(O)CH_3$;

wherein aryl is phenyl or naphthyl;

wherein -Het is a 5- or 6-membered saturated or unsaturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another heterocycle and the ring may be connected through a carbon or secondary nitrogen in the ring or an exocyclic nitrogen;

wherein $R_1$ is

a) phenyl,

b) $C_3$-$C_7$ cycloalkyl, or

c) $C_1$-$C_5$ alkyl;

wherein $R_4$ is

a) hydrogen, or

b) $C_1$-$C_5$ alkyl;

wherein $R_7$ is

a) hydroxy,

b) Het, or

c) $C_1$-$C_5$ alkyl substituted by zero to three hydroxy;

wherein $R_8$ is

a) $C_1$-$C_5$ alkyl,

b) Het, or

c) aryl;

wherein $R_{11}$ is

a) -$(CH_2)_n$- phenyl,

b) -$(CH_2)_n$-$C_3$-$C_7$ cycloalkyl, or

c) $C_1$-$C_5$ alkyl;

and pharmacologically acceptable salts thereof.

The peptides of the present invention are useful as novel human retroviral protease inhibitory peptide analogs. Therefore, the peptides inhibit retroviral proteases and thus inhibit the replication of the virus. They are useful for treating human patients infected with a human retrovirus, such as human immunodeficiency virus (strains of HIV-1 or HIV-2) or human T-cell leukemia viruses (HTLV-I or HTLV-II) which results in acquired immunodeficiency syndrome (AIDS) and/or related diseases.

The capsid and replicative enzymes (i.e. protease, reverse transcriptase, integrase) of retroviruses are translated from the viral gag and pol genes as polyproteins that are further processed by the viral protease (PR) to the mature proteins found in the viral capsid and necessary for viral functions and replication. If the PR is absent or nonfunctional, the virus cannot replicate. The retroviral PR, such as HIV-1 PR, has been found to be an aspartic protease with active site characteristics similar to those exhibited by the more complex aspartic protease, renin.

The term human retrovirus (HRV) includes human immunodeficiency virus type I, human immunodeficiency virus type II, or strains thereof, as well as human T cell leukemia virus 1 and 2 (HTLV-1 and HTLV-2) or strains apparent to one skilled in the art, which belong to the same or related viral families and which create similar physiological effects in humans as various human retroviruses.

Patients to be treated would be those individuals: 1) infected with one or more strains of a human retrovirus as determined by the presence of either measurable viral antibody or antigen in the serum and 2) in the case of HIV, having either an asymptomatic HIV infection or a symptomatic AIDS defining infection such as i) disseminated histoplasmosis, ii) isopsoriasis, iii) bronchial and pulmonary candidiasis including pneumocystic pneumonia iv) non-Hodgkin's lymphoma or v) Kaposi's sarcoma and being less than sixty years old; or having an absolute CD4+ lymphocyte count of less than 500/$mm^3$ in the peripheral blood. Treatment would consist of maintaining an inhibitory level of the peptide used according to this invention in the

patient at all times and would continue until the occurrence of a second symptomatic AIDS defining infection indicates alternate therapy is needed.

More specifically, an example of one such human retrovirus is the human immunodeficiency virus (HIV, also known as HTLV-III or LAV) which has been recognized as the causative agent in human acquired immunodeficiency syndrome (AIDS), P. Duesberg, Proc. Natl. Acad. Sci. USA, 86:755 (1989). HIV contains a retro viral encoded protease, HIV-I protease, that cleaves the fusion polypeptides into the functional proteins of the mature viral particle, E.P. Lillehoj, et al., J. Virology, 62:3053 (1988); C. Debuck, et al., Proc. Natl. Acad. Sci., 84:8903 (1987). This enzyme, HIV-I protease, has been classified as an aspartyl protease and has a demonstrated homology to other aspartyl proteases such as renin, L.H. Pearl, *et al.*, Nature 329:351 (1987); I. Katoh, *et al.*, Nature 329:654 (1987). Inhibition of HIV-I protease blocks the replication of HIV and thus is useful in the treatment of human AIDS, E.D. Clerq, J. Med. Chem. 29:1561 (1986). Inhibitors of HIV-I protease are useful in the treatment of AIDS.

Pepstatin A, a general inhibitor of aspartyl proteases, has been disclosed as an inhibitor of HIV-I protease, S. Seelmeier, *et al.*, Proc. Natl. Acad. Sci. USA, 85:6612 (1986). Other substrate derived inhibitors containing reduced bond isosteres or statine at the scissle position have also been disclosed, M.L. Moore, *et al.*, Biochem. Biophys, Res. Commun. 159:420 (1989); S. Billich, *et al.*, J. Biol. Chem. 263:17905 (1988); Sandoz, D.E. 3812-576-A.

Thus, the peptides of the present invention are useful for treating diseases caused by retroviruses, such as human acquired immunodeficiency disease syndrome (AIDS).

The peptides are also useful for treating non-human animals infected with a retrovirus, such as cats infected with feline leukemia virus. Other viruses that infect cats include, for example, feline infectious peritonitis virus, calicivirus, rabies virus, feline immunodeficiency virus, feline parvovirus (panleukopenia virus), and feline chlamydia. Exact dosages, forms and modes of administration of the peptides of the present invention to non-human animals would be apparent to one of ordinary skill in the art, such as a veterinarian.

The parent compounds and the phosphate prodrug compounds of formula I of the present invention are prepared as described in the Preparations and Examples below, or are prepared by methods analogous thereto, which are readily known and available to one of ordinary skill in the art of peptide synthesis.

CHART A

Chart A describes the preparation of the cyclic phosphate 1-Naphthoxyacetyl-L-histidyl-5S-amino-6-cyclohexyl-3R,4R-O,O-hydroxyphosphoryl-2R-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide (Formula A-3).

The solubility of compound A-1 in tetrahydrofuran is enhanced with anhydrous lithium

chloride and its reaction with di-*tert*-butyl N,N-diethylphosphoramidite in the presence of 1H-tetrazole gives the cyclic phosphite. Oxidation with *m*-chloroperbenzoic acid of this intermediate gives the corresponding cyclic phosphate A-2. The *tert*-butyl phosphate ester is removed with hydrochloric acid to give the desired cyclic phosphate A-3.

CHART B

Chart B describes the preparation of the phosphate peptide 1-Naphthoxyacetyl-L-histidyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-O-phosphate-L-seryl-2-pyridylmethylamide (Formula B-10).

Coupling of Boc-serine (B-1) with 2-pyridylmethylamine (B-2) with BOP reagent gives the adduct B-3. The *tert*-butyloxycarbonyl group is removed with trifluoroacetic acid and the resulting amine isolated as the bis trifluoroacetate salt (B-4). This amine is coupled to the known acid 5S-*tert*-butyloxycarbonylamino-4S-*tert*-butyldimethylsilyloxy-6-cyclohexyl-2S-isopropyl-hexanoic acid using BOP reagent to give compound B-5. The *tert*-butyloxycarbonyl group is removed with trifluoroacetic acid and the resulting amine B-7 is coupled to 1-naphthoxyacetyl-$N^{im}$-*tert*-butyloxycarbonyl-L-histidine (B-6) using BOP reagent to give compound B-8.

Reaction with di-*tert*-butyl N,N-diethylphosphoramidite in the presence of 1H-tetrazole gives the di-*tert*-butylphosphate B-9. Acid hydrolysis removed the *tert*-butyloxycarbonyl group, the *tert*-butyldimethylsilyl group, and the di-*tert*-butylphosphate groups to give the desired compound B-10.

CHART C

Chart C describes the preparation of the parent peptide Cyclohexanecarbonyl-4S-amino-6-cyclohexyl-3R, 4R-dihydroxy-2R-isobutyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide.

An aldol addition reaction between the aldehyde C-1 and the oxazolidinone C-2 using dibutylboron triflate and diisopropylethylamine gives the adduct C-3. The chiral auxialiary is removed by basic hydrolysis with lithium hydroxide and hydrogen peroxide to give the acid C-4. This acid C-4 is condensed with the amine L-isoleucyl-2-pyridylmethylamide C-5 using diethylphosphoryl cyanide and diisopropylethyl amine to give the product C-6. The protecting groups are removed with hydrogen chloride which is generated from acetyl chloride in methanol to give the amine C-7. Condensation of cyclohexylcarboxylic acid with the amine C-7 using diethylphosphoryl cyanide and diisopropylethyl amine gives the peptide C-8.

CHART D

Chart D describes the preparation of the parent peptide N-(4-Quinolinyl)oxyacetyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide (Formula D-5).

4-Hydroxyquinoline D-1 is alkylated with *tert*-butyl-bromoacetate using potassium hydride to give compound D-2. The *tert*-butyl ester protecting group is removed with trifluoroacetic acid to give the free acid D-3. Condensation of this acid D-3 with the amine 5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide D-4 using diethylphosphoryl cyanide and diisopropylethylamine gives the desired peptide D-5.

CHART E

Chart E describes the preparation of the parent peptides 3R-Quinuclidineaminocarbonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide (Formula E-3) and 3S-Quinuclidineaminocarbonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide (Formula E-4).

3-Aminoquinuclidine dihydrochloride is neutralized with sodium hydroxide to give the free base E-1. This amine E-1 is treated with *p*-nitrophenylchloroformate and the resulting material reacted with 5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide E-2 and diisopropylethylamine to give the two isomeric peptides E-3 and E-4.

CHARTS F - L

These charts are described in the corresponding preparations and examples below.

CHART M

Chart M describes the preparation of a biotinol C-terminus segment for coupling to the transition state insert. This segment is used in the preparation of 2-((4-([3a*S*-(3aα,4β,6aα)]-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-on-4yl)pent-1-yl)oxy)benzoyl-5*S*-amino-6-cyclohexyl-3*R*,4*R*-dihydroxy-2*R*isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine.

The compound M-1, which is commercially available or prepared by procedures described in K. N. Parameswaran, Org. Prep. Proc. Intl. 1990, 22, 119-121, is converted to the compound M-2, by using $NaBH_4$/THF/HMPA. The compound M-2 is reacted with Mesyl Cl, pyridine to obtain the compound M-3. The compound M-3 is reacted with the compound M-4, which is commercially available, in the presence of $K_2CO_3$/DMF to obtain the compound M-5. The compound M-5 is reacted with NaOH/MeOH to achieve the C-terminal segment M-6.

By a procedure analogous to that described above, the N-terminal segment, used in the preparation of 2-((4-([3a*S*-(3aα,4β,6aα)]-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-on-4yl)pent-1-yl)thio)benzoyl-5*S*-amino-6-cyclohexyl-3*R*,4*R*-dihydroxy-2*R*isopropyl-hexanoyl-L-isoleucinyl-amino-2-(4-methylthiazol-5yl)ethane, is prepared.

CHART N

Chart N describes the preparation of the methylthiazole C-termini for coupling to the transition-state insert segment. The segment N-4 is used in the preparation of 2-(2-(4-

methylthiazol-5-yl)ethyl)oxy)benzoyl-5*S*-amino-6-cyclohexyl3*R*,4*R*-dihydroxy-2*R*-isopropyl-hexanoyl-L-isoleucinyl-2aminomethylpyridine and 2-(2-(4-methylthiazol-5-yl)ethyl)oxy)benzoyl-5*S*-amino-6-cyclohexyl3*R*,4*R*-dihydroxy-2*R*-isopropyl-hexanoyl-L-isoleucinyl-1-aminoethyl(4methylthiazole). The segment N-9 is used in the preparation of 2-(2-(4-methylthiazol-5-yl)ethyl)thio)benzoyl-5*S*-amino-6cyclohexyl-3*R*,4*R*-dihydroxy-2*R*-isopropyl-hexanoyl-L-isoleucinyl-2aminomethylpyridine and 2-(2-(4-methylthiazol-5-yl)ethyl)thio)benzoyl-5*S*-amino-6cyclohexyl-3*R*,4*R*-dihydroxy-2*R*-isopropyl-hexanoyl-L-isoleucinyl 1aminoethyl(4-methylthiazole).

The compound N-1 is reacted with the compound N-2, both of which are commercially available, in the presence of: $PrO_2CN{=}NCO_2iPr/PPh_3$/THF, to obtain the compound N-3. The compound N-3 is reacted with NaOH/MeOH to achieve the compound N-4.

The compound N-5, which is commercially available, is reacted with $PBr_3$/pyridine to obtain the compound N-6. The compound N-6 is reacted with the compound N-7, in the presence of $K_2CO_3$/DMF to obtain the compound N-8. The compound N-8 is converted to the compound N-9 by using NaOH/MeOH.

CHART O

Chart O describes the preparation of the (3R,4R)-Leu $\psi$ [CH(OH)CH(OH)] Dehydroleu insert by a diastereoselective aldol (D.A. Evans, et al., Tetrahedron Lett. 1986, 27, 4957-4960), C-terminus functionalization and protecting group removal.

The compound O-1 is reacted with $(EtO)_2P(O)CH_2CO_2Et$/NaH (S.V. Kellar, et al., Syn. Commun. 1990, 20, 839) to obtain the compound O-2 (Reg. No. 2351-97-5). The compound O-2 is converted to the compound O-3 (Reg. No. 16666-43-6) by using NaOH/ $H_2O$. The compound O-3 is reacted first with $(COCl)_2$ and then with BuLi, compound O-4 (Reg. No. 77943-39-6) to give the compound O-5. The compound O-5 is reacted first with BuOTf, then with $NEt_3$ and finally with the compound O-6 (Reg. No. 107599-97-3) (Thaisrivongs, et al., J. Med. Chem. 1987, 30, 976) to yield the compound O-7. The compound O-7, reacted with LiOH, gives the compound O-8. The compound O-8 is reacted with the compound O-9 using $(EtO_2)P(O)CN$ to give the compound O-10. The compound O-10 is converted to the compound O-11 by means of acid solvolysis. This insert O-11 may then by coupled to the amino terminus segment of a peptide by procedures readily known and available to one of ordinary skill in the peptide synthesis art.

As is apparent to those of ordinary skill in the art, the compounds of the present invention can occur in several diastereomeric forms, depending on the configuration around the asymmetric carbon atoms. All such diastereomeric forms are included within the scope of the present invention. Preferably, the stereochemistry of the amino acids corresponds to that of the naturally occurring amino acids.

The present invention provides for compounds of formula I or pharmacologically acceptable salts and/or hydrates thereof. Pharmacologically acceptable salts refers to those salts which would be readily apparent to a manufacturing pharmaceutical chemist to be equivalent to the parent compound in properties such as formulation, stability, patient acceptance and bioavailablility.

The compounds of the present invention are useful for treating patients infected with human immunodeficiency virus (HIV) which results in acquired immunodeficiency syndrome (AIDS) and related diseases. For this indication, they are administered by oral, nasal, transdermal and parenteral (including i.m. and i.v.) routes in doses of 1 mg to 100 mg/kg of body weight.

Those skilled in the art would know how to formulate the compounds of this invention into appropriate pharmaceutical dosage forms. Examples of the dosage forms include oral formulations, such as tablets or capsules, or parenteral formulations, such as sterile solutions.

When the compounds in this invention are administered orally, an effective amount is from about 1 mg to 100 mg per kg per day. Either solid or fluid dosage forms can be prepared for oral administration. Solid compositions are prepared by mixing the compounds of this invention with conventional ingredients such as talc, magnesium stearate, dicalcium phosphate, magnesium aluminum silicate, calcium sulfate, starch, lactose, acacia, methyl cellulose, or functionally similar pharmaceutical diluents and carriers. Capsules are prepared by mixing the compounds of this invention with an inert pharmaceutical diluent and placing the mixture into an appropriately sized hard gelatin capsule. Soft gelatin capsules are prepared by machine encapsulation of a slurry of the compounds of this invention with an acceptable inert oil such as vegetable oil or light liquid petrolatum. Syrups are prepared by dissolving the compounds of this invention in an aqueous vehicle and adding sugar, aromatic flavoring agents and preservatives. Elixirs are prepared using a hydroalcoholic vehicle such as ethanol, suitable sweeteners such as sugar or saccharin and an aromatic flavoring agent. Suspensions are prepared with an aqueous vehicle and a suspending agent such as acacia, tragacanth, or methyl cellulose.

When the compounds of this invention are administered parenterally, they can be given by injection or by intravenous infusion. An effective amount is from about 1 mg to 100 mg per kg per day. Parenteral solutions are prepared by dissolving the compounds of this invention in water and filter sterilizing the solution before placing in a suitable sealable vial or ampule. Parenteral suspensions are prepared in substantially the same way except a sterile suspension vehicle is used and the compounds of this invention are sterilized with ethylene oxide or suitable gas before it is suspended in the vehicle.

The exact route of administration, dose, or frequency of administration would be readily determined by those skilled in the art and is dependant on the age, weight, general

physical condition, or other clinical symptoms specific to the patient to be treated.

Patients to be treated would be those individuals: 1) infected with one or more than one strain of a human immunodeficiency virus as determined by the presence of either measurable viral antibody or antigen in the serum and 2) having either an asymptomatic HIV infection or a symptomatic AIDS defining infection such as i) disseminated histoplasmosis, ii) isoporiasis, iii) bronchial and pulmonary candidiasis including pneumocystis pneumonia, iv) non-Hodgkin's lymphoma, or v) Kaposi's sarcoma and being less than sixty years old; or having an absolute CD4+ lymphocyte count of less than 500/$mm^3$ in the peripheral blood. Treatment would consist of maintaining an inhibitory level of the compounds of this invention in the patient at all times and would continue until the occurrence of a second symptomatic AIDS defining infection indicates alternate therapy is needed.

The utility of representative compounds of the present invention has been demonstrated in several biological tests as described below.

The HIV-1 protease has been expressed in E. coli, isolated, characterized and used to determine the inhibitory constants ($K_I$) of potential inhibitory compounds as follows:

The synthetic peptide H-Val-Ser-Gln-Asn-Tyr-Pro-Ile-Val-OH serves as the substrate for the measurement of HIV-1 protease activity. This peptide corresponds to the sequence from residue 128 to 135 in the HIV gag protein. Cleavage of the synthetic peptide, as well as the gag protein, takes place at the Tyr-Pro bond. HIV-1 protease activity is measured at 30°C in 50 mM sodium acetate, pH 5.5, containing 10% glycerol, 5% ethylene glycol, 0.1% Nonidet P-40 and 2.8 mM substrate in a total volume of 50 $\mu$l. After 30 minutes of incubation, 75 $\mu$l of 1% trifluoroacetic acid (TFA) is added and the reaction mixture subjected to HPLC analysis. HPLC is carried out with a Vydac $C_{18}$ column (0.46 x 15 cm), eluting with a linear gradient of 0-30% acetonitrile over a period of 25 minutes at a flow rate of 1.0 ml/minute.

The $K_i$ values of representative compounds of the present invention are listed in the preparations below.

Some of the compounds of the present invention have been further evaluated in a CV-1 cellular assay described below, where it was demonstrated that the retrovirus-inhibiting effect was due to the inhibition of HIV-1 protease.

CV-1 cells were seeded at 2 x $10^{-5}$ cells/well in 24 well Costar dishes and infected 6 to 12 hours later with vVK-1 at 5 PFU/cell (V. Karacostas, et al., "Human Immunodeficiency Virus-Like Particles Produced by a Vaccinia Virus Expression Vector (retrovirus/AIDS/virus assembly/reverse transcriptase," Proc. Natl. Acad. Sci., USA, 1989). The test compounds were dissolved in DMSO containing 2.5% fetal bovine serum and added to triplicate wells immediately after virus addition. Twenty-four hours after infection the culture medium was removed, the monolayer washed with 1 ml of PBS and the cells lysed by the addition of 0.1 ml

of loading buffer (62.5 mM Tris-H Cl pH 6.8, 2.3% SDS, 5% B-mercaptoethanol, 10% glycerol). The cells lysates were collected individually, placed in boiling water for 3 minutes, and then 0.025 ml of each is subjected to electrophoresis on 12% SDS-polyacrylamide gels. The proteins were electroblotted onto nitrocellulose and analyzed by Western blotting. The primary antibodies were sheep anti-Pr24 and sheep anti-Pr17 and the secondary antibody in both cases was alkaline-phosphatase conjugated rabbit-anti sheep IgG (all obtained from Kirkegaard & Perry Laboratories, Gaithersburg, MD).

Test compounds significantly inhibited proteolysis of the HIV-1 gag polyprotein (Pr55) to the mature viral structural proteins Pr24 and Pr17 in the above cells infected with the recombinant vaccina virus expressing the HIV-1 gag-pol genes. The HIV-1 like particles released from inhibitor-treated cells contained almost exclusively Pr55 and other gag precursors, but not Pr24.

The % inhibition values of representative compounds are listed in the examples below.

The following compounds of the present invention are preferred:

1-naphthoxyacetyl-O-phosphoryl-L-threonyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine, dipotassium salt; or Noa-O-$PO_3K_2$-Thr-CVA-Ile-Amp;

1-naphthoxyacetyl-O-phosphoryl-L-seryl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine, dipotassium salt; or Noa-O-$PO_3K_2$-Ser-CVA-Ile-Amp;

Nα-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-(O-phosphoryl)-2-isopropyl-1-oxohexyl]-N-(2-benzimidazolylmethyl)-L-isoleucinamide, trifluoroacetic acid salt; or 2Py CO CVP Ile Amb;

Nα-[(2S,4S,5S)-5-[N-[(3-Pyridinyl)methoxycarbonyl]amino]-6-cyclohexyl-4-(O-phosphoryl)-2-isopropyl-1-oxohexyl]-N-(2-benzimidazolylmethyl)-L-isoleucinamide, trifluoroacetic acid salt; or 3Poc CVP Ile Amb;

N-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-(O-phosphoryl)-2-isopropyl-1-oxohexyl]-N-[(1S,2R)-2-hydroxy-1-indanyl]amine, trifluoroacetic acid salt; or 2Py CO CVP Ahi;

N-[(2S,4S,5S)-5-[N-[2-(3-Pyridinyl)ethenylcarbonyl]amino]-6-cyclohexyl-4-(O-phosphoryl)-2-isopropyl-1-oxohexyl]-N-[(1S,2R)-2-hydroxy-1-indanyl]amine; or 3Py CH=CHCO CVP Ahi;

3-(O-phosphoryl-4-OH-phenyl)-butyryl-L-histidyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Dat(O-$PO_3H_2$)-His-CVA-Ile-Amp;

$N_\alpha$-[(2S,4S,5S)-5-[N-[$N_\alpha$-(1-Naphthalenyloxyacetyl)-L-histidyl]amino-6-cyclohexyl-4-

(O-phosphoryl)-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide, trifluoroacetic acid salt; or NOA-His-($OPO_3H_2$)CVA-Ile-Amp;

1-Naphthoxyacetyl-L-histidyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-O-phosphate-L-seryl-2-pyridylmethylamide;

$N_\alpha$-[(2S,4S,5S)-5-[N-(2-pyridinyl carbonyl)amino]-6-cyclohexyl-4-(O-phosphoryl)-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide trifluoroacetic acid salt; or 2-pyridinyl carbonyl-($OPO_3H_2$)CVA-Ile-Amp;

$N_\alpha$-[(2S,4S,5S)-5-[N-(2-pyridinyl carbonyl)amino]-6-cyclohexyl-4-(O-phosphoryl)-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide hydrochloride salt; and

Nα-[(2S,4S,5S)-5-[N-[2-[2-[2-(2-Methoxyethoxy)ethoxy]ethoxy]phenylcarbonyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-benzimidazolylmethyl)-L-isoleucinamide; or Mee CVP Ile Amb.

The most preferred compounds of the present invention are the following:

1-naphthoxyacetyl-O-phosphoryl-L-threonyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine, dipotassium salt; or Noa-O-$PO_3K_2$-Thr-CVA-Ile-Amp;

1-naphthoxyacetyl-O-phosphoryl-L-seryl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine, dipotassium salt; or Noa-O-$PO_3K_2$-Ser-CVA-Ile-Amp; and

Nα-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-(O-phosphoryl)-2-isopropyl-1-oxohexyl]-N-(2-benzimidazolylmethyl)-L-isoleucinamide, trifluoroacetic acid salt; or 2Py CO CVP Ile Amb.

The preferred parent compounds of the prodrug compounds of the present invention are:

1-Noa-His-Cha PSI[CHOHCHOH]Val-Ile-Amp; or 1H-Imidazole-4-propanamide, N-[1-(cyclohexylmethyl)-2,3-dihydroxy-5-methyl-4-[[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]-[amino]carbonyl]hexyl]-α-[[(1-naphthalenyloxy)-acetyl]amino]-, [1S-[1R*(R*),2S*,3S*,4S*(1R*,2R*)]]-; or NOA-His-CVD-Ile-Amp;

((5-(3,6,9,12,15-pentaoxa-hexadec-1-yl)oxy)naphthalen-1yl)oxyacetyl-L-valinyl-5*S*-amino-6-cyclohexyl-3*R*,4*R*-dihydroxy-2*R*isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine; or 5-PentaegNoa-Val-CVD-Ile-Amp;

1-naphthoxyacetyl-L-threonyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Noa-Thr-CVA-Ile-Amp;

1-naphthoxyacetyl-L-seryl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Noa-Ser-CVA-Ile-Amp;

1-naphthoxyacetyl-L-threonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-

hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Noa-Thr-CVD-Ile-Amb;

1-naphthoxyacetyl-L-seryl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Noa-Ser-CVD-Ile-Amb;

((5-(8-amino-3,6-dioxa-oct-1-yl)oxy)naphthalen-1-yl)oxyacetyl-L-valinyl-5*S*-amino-6-cyclohexyl-3*R*,4*R*-dihydroxy-2*R*-isopropylhexanoyl-L-isoleucinyl-2-aminomethylpyridine;

2-[2-(2-(2-methoxy)ethoxy)ethoxy)ethoxy]benzoyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Mee-CVD-Ile-Amb;

1-naphthoxyacetyl-L-threonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-1S-amino-2R-hydroxy-indane; or Noa-Thr-CVD-Ahi;

1-naphthoxyacetyl-L-seryl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-1S-amino-2R-hydroxy-indane; or Noa-Ser-CVD-Ahi;

1-naphthoxyacetyl-L-histidyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-1S-amino-2R-hydroxy-indane; or Noa-His-CVD-Ahi;

3-(4-hydroxyphenyl)-butyryl-L-valyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Dat-Val-CVA-Ile-Amb;

4-morpholinecarbonyl-L-valyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Morph-Val-CVA-Ile-Amp; and

2-[(2-phenoxy)ethoxy]benzoyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Peb-CVD-Ile-Amb.

## DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the Preparations and Examples below and throughout this document:

$^1$H-NMR is nuclear magnetic resonance;

Aai is 1S-amino-2R acetoxy-indane;

Ac is acetyl;

Acb is 2-acetoxybenzoyl;

AcO is acetyloxy;

Ahi is 1S-amino-2R-hydroxy-indane;

Amb is 2-aminomethylbenzimidazole;

Amp is 2-(aminomethyl) pyridine;

Amp-NO is (2-pyridylmethyl) amino (pyridine N-oxide);

Apb is 4-[(3-amino-2-pyridinyl)amino]-2-butenyl-amine;

Ape is 2-[(3-amino-2-pyridinyl)amino]ethylamine;

Apr is 2-(2-pyridinylamino)-ethylamide;

Asn is asparagine;

Biotinoyl is 4-([3aS-(3a$\alpha$,4$\beta$,6a$\alpha$)]-1H-thieno[3,4-d]imidazolyl)-pentanoyl-;

Boc is t-butoxycarbonyl;

BOC-ON is 2-(tert-butoxycarbonyl-oxyimino)-2-phenylacetonitrile;

BOP is benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate;

BroP is Bromo tris (dimethylamino) phosphonium hexafluorophosphate;

Bz or Bzl is benzyl;

C is centigrade;

Cbz is benzyloxycarbonyl;

CcD is the moiety of formula X wherein $R_1$, is cyclohexyl, $R_2$, is α-hydroxy, $R_4$, is α-hydroxy and $R_3$ is β-$CH_2$-cyclohexyl;

CCD is the moiety of formula X wherein $R_1$, is cyclohexyl, $R_2$, is α-hydroxy, $R_3$ is α-$CH_2$-cyclohexyl and $R_4$, is α-hydroxy;

$CDCl_3$ is deuteriochloroform;

Celite is a filter aid;

CVA is Cha$\Psi$[CH(OH)$CH_2$]Val of formula X wherein $R_1$, is cyclohexyl, $R_2$, is hydrogen, $R_3$ is α-isopropyl and $R_4$, is α-hydroxy and is preferably 5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl;

chpVA is the moiety of formula X wherein $R_1$, is cycloheptyl, $R_2$, is hydrogen, $R_3$ is α-isopropyl, and $R_4$, is α-hydroxy;

CLA is the moiety of formula X wherein $R_1$, is cyclohexyl, $R_2$, is hydrogen, $R_3$ is -α-isobutyl, and $R_4$, is α-hydroxy;

CLD is the moiety of formula X wherein $R_1$, is cyclohexyl, $R_2$, is α-hydroxy, $R_4$, is α-hydroxy and $R_3$ is α-isobutyl;

CPD is the moiety of formula X wherein $R_1$, is cyclohexyl, $R_2$, is α-hydroxy, $R_4$, is α-hydroxy and $R_3$ is α-benzyl;

CVD is the moiety of formula X wherein $R_1$, is cyclohexyl, $R_2$, is α-hydroxy, $R_3$ is α-isopropyl and $R_4$, is α-hydroxy and is preferably 5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl;

CVD' is the moiety of formula X wherein $R_1$, is cyclohexyl, $R_2$, is β-hydroxy, $R_4$, is α-hydroxy, and $R_3$ is α-isopropyl;

CVP or ($OPO_3H_2$)CVA is 5S-amino-6-cyclohexyl-4S-(O-phosphoryl)-2S-isopropyl-hexanoyl;

DANS is dansyl or 5-dimethylaminonaphthalenesulfonyl;

Dat is des-amino-tyrosine;

DCC is dicyclohexylcarbodiimide;

DEPC is diethylphosphoryl cyanide;

Des-amino-tyrosine ($OPO_3H_2$) means the hydrogen atom of the hydroxy group of the

des-amino tyrosine amino acid is substituted by $-OPO_3H_2$;

DIPEA is N,N-diisopropylethylamine;

DMF is N,N-dimethylformamide;

DMSO is dimethylsulfoxide;

DNP is 2,4-dinitrophenyl;

$ET_3N$ is triethylamine;

$ET_20$ is diethylether;

Et0Ac is ethyl acetate;

FAB is fast atom bombardment;

g is grams;

Glu is glutamine;

δ-Glu is δ-glutamyl acid;

Gly is glycine;

Gln is glutamine;

Hexaeg is hexa(ethyleneglycol);

His is L-histidine;

Hmb is 2-hydroxy-3-methyl-butyryl;

Hyb is 2-hydroxybenzoyl;

N-MeHis is Nα-methyl histidine;

HOBT is 1-hydroxybenzotriazole;

HOAc is acetic acid;

Hpa is 2-hydroxyphenethylamine at the C-terminus or is hydroxyphenylacetyl at the N-terminus;

HPLC is high performance liquid chromatography;

Hsr is L-homoserine;

Ile is L-isoleucine;

IR is infrared spectrum;

Iva is isovaleryl;

LCA is the moiety of formula X wherein $R_1$ is isopropyl, $R_2$ is hydrogen, $R_3$ is -α-$CH_2$-cyclohexyl and $R_4$ is α-hydroxy;

LFA is the difluoro ketone version of statine analogue as described more fully in PCT Pub. No. WO86/06379 (6 November 1985), and is the moiety of formula IV wherein $R_1$ is cyclohexylmethyl;

LFD is -L-Leu-[R,R-CH(OH)CH(OH)Phe- or 5S-amino-2S-benzyl-3R,4R-dihydroxy-7 methyl-octanoyl;

LLA is the moiety of formula X wherein $R_1$ is isopropyl, $R_2$ is hydrogen, $R_3$ is -α-

isobutyl, and $R_4$ is $\alpha$-hydroxy;

LID is the moiety of formula X wherein $R_1$ is isopropyl, $R_2$ is $\beta$-hydroxy, $R_4$ is $\beta$-hydroxy and $R_3$ is $\beta$-isobutyl;

LLd is the moiety of formula X wherein $R_1$ is isopropyl, $R_2$ is $\alpha$-hydroxy, $R_4$ is $\alpha$-hydroxy, and $R_3$ is $\beta$-isobutyl;

LLD is the moiety of formula X wherein $R_1$ is isopropyl, $R_2$ is $\alpha$-hydroxy, $R_4$ is $\alpha$-hydroxy, and $R_3$ is $\alpha$-isobutyl;

LPA is the moiety of formula X wherein $R_1$ is isopropyl, $R_2$ is hydrogen, $R_3$ is -$\alpha$-benzyl and $R_4$ is $\alpha$-hydroxy;

LVA is Leu$\Psi$(CH(0H)$CH_2$)Val with the S configuration at C4 (the hydroxyl-bearing carbon atom) of the formula X wherein $R_1$ is isopropyl, $R_2$ is hydrogen, $R_3$ is $\alpha$-isopropyl and $R_4$ is $\alpha$-hydroxy;

LVD is the diol version of LVA as described more fully in PCT Pub. No. WO87/05302 (11 September 1987) and is the moiety of formula X wherein $R_1$ is isopropyl, $R_2$ is $\alpha$-hydroxy, $R_4$ is $\alpha$-hydroxy and $R_3$ is $\alpha$-isopropyl;

LVDA′ is the moiety of formula X wherein $R_1$ is isopropyl, $R_2$ is $\beta$-hydroxy, $R_4$ is $\alpha$-hydroxy, and $R_3$ is $\alpha$-isopropyl;

M or mol is mole;

Mba is 2S-methylbutylamine;

Me is methyl;

Meb is 2-[(2-methoxy)ethoxy]benzoyl;

Mee is 2-[2-(2-(2-methoxy)ethoxy)ethoxy)ethoxy]benzoyl;

MeOH is methanol;

Mep is 3-[2-(2-methoxy)ethoxy)ethoxy]pyridyl-2-carbonyl;

ml is milliliter;

Moc is methoxycarbonyl;

Morph is 4-morpholinecarbonyl;

Mpb is 4-methyl-2-[(2-phenoxy)ethoxy]benzoyl;

Mpc is 3-[2-(2-(2-methoxy)ethoxy)ethoxy)ethoxy]pyridyl-2-carbonyl;

MPLC is medium pressure liquid chromatography;

MS is mass spectroscopy;

Mtb is 2-[2-(2-methoxy)ethoxy)ethoxy]benzoyl;

Npb is 4-[(3-nitro-2-pyridinyl)amino]-2-butenylamine;

Npe is 2-[(3-nitro-2-pyridinyl)amino]ethylamine;

NOA is (1-naphthyloxy)acetyl;

O-phosphoryl is -$OPO_3H_2$;

$OPO_3K_2$-Ser means the hydrogen atom of the hydroxy group of the serine amino acid is substituted by -$OPO_3K_2$;

$OPO_3K_2$-Thr means the hydrogen atom of the hydroxy group of the threonine amino acid is substituted by -$OPO_3K_2$;

Peb is 2-[(2-phenoxy)ethoxy]benzoyl;

Pentaeg is penta(ethyleneglycol);

Pep is 3-[(2-phenoxy)ethoxy]propionyl or is 2-[(2-phenoxy)ethoxy]benzoyl;

Ph is phenyl;

Phe is phenylalanine;

POA is phenyloxyacetyl;

2 Poc is (2-pyridinyl)methoxycarbonyl;

3 Poc is (3-pyridinyl)methoxycarbonyl;

4 Poc is (4-pyridinyl)methoxycarbonyl;

Ppc is 3-[2-(phenoxy)ethoxy]pyridyl-2-carbonyl;

PPD is the moiety of formula X wherein $R_1$ is phenyl, $R_2$ is $\alpha$-hydroxy, $R_4$ is $\alpha$-hydroxy and $R_3$ is $\alpha$-benzyl;

Pro is L-proline;

Ptb is 2-[(phenylthio)methoxy]benzoyl;

Ptc is 3-[(phenylthio)methoxy]pyridyl-2-carbonyl;

2 Py is 2-pyridinyl;

3 Py is 3-pyridinyl;

2-Py-Ala is D,L-(3-pyridyl)-alanine;

Ser is L-serine;

TBA or Tba is t-butylacetyl;

TBDMS is tert-butyldimethylsilyl;

TBAP is tetra-n-butylammonium phosphate;

TEA is triethylamine;

TFA is trifluoroacetic acid;

THF is tetrahydrofuran;

Thr is L-threonine;

TLC is thin layer chromatography;

Tma is *tert*-butylmethylamine;

Tos is p-toluenesulfonyl;

Trieg is tri(ethyleneglycol);

TsOH is p-toluenesulfonic acid;

Tyr is tyrosine;

($OCH_3$)Tyr is O-methyl tyrosine; and

Val is L-valine.

In formula X, wherein the variables are as defined above, "$\alpha$" is used to indicate the substituent is below the plane of the drawing and "$\beta$" is used to indicate the substituent is above the plane of the drawing.

The wedge-shape line indicates a bond which extends above the plane of the paper relative to the plane of the compound thereon.

The dotted line indicates a bond which extends below the plane of the paper relative to the plane of the compound thereon.

The following Preparations and Examples illustrate the present invention:

PREPARATIONS 1-106

Using the chemical procedures, starting materials, and reactants described in International Application, PCT/US90/05818, filed 16 October 1990, pages 34-57, which is incorporated by reference herein, or methods analogous thereto, all of which are readily known and available to one of ordinary skill in the art, the following parent compounds of the present invention, having the indicated physical characteristics, are prepared:

(1) L-Isoleucinamide, N-(5-amino-4-hydroxy-7-methyl-2-(1-methylethyl)-1-oxooc-tyl]-N-(2-pyridinylmethyl)-, trifluoroacetate, (S,S,S)-; or H-LVA-Ile-Amp;

(2) 1H-Imidazole-4-propanamide, N-[2-hydroxy-5-methyl-1-(2-methylpropyl)-4-[[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]amino]carbonyl]hexyl]-$\alpha$-[(phenoxyacetyl)-amino]-, [1S-[1R*,2R*,4R*(1R*,2R*)]]- ; or POA-His-LVA-Ile-Amp;

(3) 1H-Imidazole-4-propanamide, N-[1-(cyclohexylmethyl)-3,3-difluoro-4-[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]amino]-2,4-dioxobutyl]-$\alpha$-[[(1-naphthalenyloxy)acetyl]amino]-, [1S-(1R*($\alpha$R*),2R*]]-; or NOA-His-LFA-Ile-Amp;

(4) 1H-Imidazole-4-propanamide, $\alpha$-[[2-(acetyloxy)-3-(1-naphthalenyl)-1-oxopropyl]amino]-N-[1-(cyclohexylmethyl)-3,3-difluoro-4-[[2-methyl-1-[[(2-pyridinyl-methyl)amino]carbonyl]butyl]amino]-2,4-dioxobutyl]-, [1S-[1R*[$\alpha$R*(R*)],2R*]]-;

(5) L-Histidinamide, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-[1-(cyclohexylmethyl)-3,3-difluoro-4-[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]-butyl]amino]-2,4-dioxobutyl]-; or Boc-Phe-His-LFA-Ile-Amp;

(6) 1H-Imidazole-4-propanamide, N-[1-(cyclohexylmethyl)-2-hydroxy-6-methyl-4-[[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]amino]carbonyl]heptyl]-$\alpha$-[(phenoxyacetyl)amino]-, [1S-[1R*(R*),2R*,4S*(1R*,2R*)]]-; or POA-His-CLA-Ile-Amp;

(7) 1H-Imidazole-4-propanamide, N-[2,3-dihydroxy-5-methyl-1-(2-methylpropyl)-4-[[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]amino]carbonyl]hexyl]-$\alpha$-[(phenoxyacetyl)amino]- [1S-[1R*(R*),2S*,3R*,4R*(1R*,2R*)]]-; or POA-His-LVDA-Ile-Amp;

(8) 1H-Imidazole-4-propanamide, N-[2,3-dihydroxy-5-methyl-4-[[(2-methylbutyl)amino]carbonyl]-1-(2-methylpropyl)hexyl]-α-[(phenoxyacetyl)amino]-, [1R-[1R*(S*),2S*,3S*,4S*(S*)]]-; or POA-His-LVDA-Mba;

(9) Boc-Phe-His-Cha psi[CHOHCHOH]Val-Ile-Amp; or L-Histidinamide, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-[1-(cyclohexylmethyl)-2,3-dihydroxy-5-methyl-4-[[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]amino]carbonyl]hexyl]-, [1S-[1R*,2S*,3S*,4S*(1R*,2R*)]]-; or BOC-Phe-His-CVD-Ile-Amp;

(10) 1-Noa-His-Cha PSI[CHOHCHOH]Val-Ile-Amp; or 1H-Imidazole-4-propanamide, N-[1-(cyclohexylmethyl)-2,3-dihydroxy-5-methyl-4-[[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]-[amino]carbonyl]hexyl]-α-[[(1-naphthalenyloxy)-acetyl]amino]-, [1S-[1R*(R*),2S*,3S*,4S*(1R*,2R*)]]-; or NOA-His-CVD-Ile-Amp;

(11) 1H-Imidazole-4-propanamide, N-[2-hydroxy-6-methyl-1-(2-methylpropyl)-4-[[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]amino]carbonyl]heptyl]-α-[(phenoxyacetyl)amino]-, [1S-[1R*(R*),2R*,4S*(1R*,2R*)]]-; or POA-His-LLA-Ile-Amp;

(12) 1H-Imidazole-4-propanamide, N-[2-hydroxy-1-(2-methylpropyl)-5-[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]amino]-5-oxo-4-(phenylmethyl)pentyl]-α-[(phenoxyacetyl)amino]-, [1S-[1R*(R*),2R*,4S*,5(1R*,2R*)]]-; or POA-His-LPA-Ile-Amp;

(13) 1H-Imidazole-4-propanamide, N-[4-(cyclohexylmethyl)-2-hydroxy-1-(2-methylpropyl)-5-[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]amino]-5-oxopentyl]-α-[(phenoxyacetyl)amino]-, [1S-[1R*(R*),2R*,4S*,5(1R*,2R*)]]-; or POA-His-LCA-Ile-Amp;

(14) L-Histidinamide, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-[2-hydroxy-1-(2-methylpropyl)-5-[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]amino--5-oxo-4-(phenylmethyl)pentyl]-, [1S-[1R*,2R*,4S*,5(1R*,2R*)]]-; or Boc-Phe-His-LPA-Ile-Amp;

(15) L-Histidinamide, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-[4-(cyclohexylmethyl)-2-hydroxy-1-(2-methylpropyl)-5-[[2-methyl-1-[[(2-pyridinylmethyl)-amino]carbonyl]butyl]amino]-5-oxopentyl]-, [1S-[1R*,2R*,4S*,5(1R*,2R*)]]-; or Boc-Phe-His-LCA-Ile-Amp;

(16) L-Talonamide, 6-cyclohexyl-2,5,6-trideoxy-5-[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-L-histidyl]amino]-2-(1-methylethyl)-N-[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]-, [S-(R*,R*)]-; or Boc-Phe-His-CVD'-Ile-Amp;

(17) L-Histidinamide, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-(2,3-dihydroxy-5-methyl-1-(2-methylpropyl)-4-[[(2-methyl-1-[[(2-pyridinylmethyl)-amino]carbonyl]butyl]amino]carbonyl]hexyl]-, [1S-[1R*,2S*,3R*,4-Amp; or Boc-Phe-His-LVDA'-Ile-Amp; FAB-MS: $[m + H]^+$ at 835.5084;

(18) 4-Morpholinebutanamide, ß-hydroxy-N-[2-[[2-hydroxy-5-methyl-1-(2-methylpropyl)-4-[[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]amino]-

carbonyl]hexyl]amino]-1-(1H-imidazol-4-ylmethyl)-2-oxoethyl]-α-(1-naphthalenylmethyl)-τ-oxo-, [1S-[1R*[R*(αS*,ßR*)],2R*,4R*(1R*,2R*)]]-;

(19) 1H-Imidazole-4-propanamide, N-[1-(cyclohexylmethyl)-2-hydroxy-5-methyl-4-[[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]amino]carbonyl]hexyl]-α-[(phenoxyacetyl)amino]-, [1S-[1R*(R*),2R*,4R*(1R*,2R*)]]-; or POA-His-CVA-Ile-Amp; FAB-MS: $[m + H]^+$ at 746.4598;

(20) 1H-Imidazole-4-propanamide, α-[[[5-(dimethylamino)-1-naphthalenyl]sulfonyl]amino]-N-[2-hydroxy-5-methyl-1-(2-methylpropyl)-4-[[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]amino]carbonyl]hexyl]-, [1S-[1R*(R*),2R*,-4R*(1R*,2R*)]]-; or DANS-His-LVA-Ile-Amp;

(21) 1H-Imidazole-4-propanamide, N-[1-(cycloheptylmethyl)-2-hydroxy-5-methyl-4-[[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]amino]carbonyl]hexyl]-α-[(phenoxyacetyl)amino]-, [1S-[1R*(R*),2R*,4R*(1R*,2R*)]]-; or POA-His-chpVA-Ile-Amp;

(22) L-Histidinamide, N-[[5-(dimethylamino)-1-naphthalenyl]sulfonyl]-L-phenylalanyl-N-[2-hydroxy-5-methyl-1-(2-methylpropyl)-4-[[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]amino]carbonyl]hexyl]-, [1S-[1R*,2R*,4R*(1R*,2R*)]]-; or DANS-Phe-His-LVA-Ile-Amp;

(23) Octanamide, 5-[(3,3-dimethyl-1-oxobutyl)amino]-4-hydroxy-7-methyl-2-(1-methylethyl)-N-[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]-, [2S-[1(1R*,2R*),2R*,4R*,5R*]]-; or TBA-LVA-Ile-Amp; FAB-MS: $[m + H)^+$ at 533;

(24) Cyclohexanehexanamide, δ-[(3,3-dimethyl-1-oxobutyl)amino]-τ-hydroxy-α-(1-methylethyl)-N-[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]-, [αS-[N(1R*,2R*),αR*,τR*,δR*]]-; or TBA-CVA-Ile-Amp; FAB-MS: $[m + H]^+$ at 573;

(25) 1H-Imidazole-4-propanamide, α-amino-N-[2-hydroxy-5-methyl-1-(2-methylpropyl)-4-[[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]amino]-carbonyl]hexyl]-, [1S-[1R*(R*),2R*,4R*(1R*,2R*)]]; or H-His-LVA-Ile-Amp;

(26) L-Histidinamide, L-phenylalanyl-N-[2-hydroxy-5-methyl-1-(2-methylpropyl)-4-[[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]amino]carbonyl]hexyl]-, [1S-(1R*,2R*,4R*(1R*,2R*)]]-; or H-Phe-His-LVA-Ile-Amp;

(27) Cyclohexanehexanamide, δ-amino-τ-hydroxy-α-(1-methylethyl)-N-[[2-methyl-1-[[(2-pyridinylmethyl)]amino]carbonyl]butyl]-, dihydrochloride, [αS-[N(1R*,2R-*),αR*,τR*,δR*]]-; or H-CVA-Ile-Amp; FAB-MS: $[m + H]^+$ at 475;

(28) Cyclohexanehexanamide, δ-(acetylamino)-τ-hydroxy-α-(1-methylethyl)-N-[2-methyl-1-[[(pyridinylmethyl)amino]carbonyl]butyl], [αS-[N(1R*,2R*),αR*,τR*,δR*]]-; or Ac-CVA-Ile-Amp; FAB-MS: $[m + H]^+$ at 517;

(29) Octanamide, 5-(acetylamino)-4-hydroxy-7-methyl-2-(1-methylethyl)-N-[2-

methyl-1-[[(2-pyridinylmethyl)amino)carbonyl]butyl]-, [2S-[N(1R*,2R*),2R*,4R*,5R*]]-, monoacetate (salt); or Ac-LVA-Ile-Amp; FAB-MS: $[m + H]^+$ at 477;

(30) L-Valinamide, L-phenylalanyl-N-[2-hydroxy-5-methyl-1-(2-methylpropyl)-4-[[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]amino]carbonyl]hexyl]-, [1S-[1R*,2R*,4R*(1R*,2R*)]]-; or H-Phe-Val-LVA-Ile-Amp;

(31) Octanamide, 5-[[2-(acetylamino)-3-methyl-1-oxobutyl]amino]-4-hydroxy-7-methyl-2-(1-methylethyl)-N-[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]-, [2S-[N(1R*,2R*),2R*,4R*,5R*(R*)]]-, monoacetate (salt); or Ac-Val-LVA-Ile-Amp; FAB-MS: $[m + H]^+$ at 576;

(32) L-Valinamide, L-valyl-N-[2-hydroxy-5-methyl-1-(2-methylpropyl)-4-[[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]amino]carbonyl]hexyl]-, [1S-[1R*,2R*,4R*(1R*,2R*)]]-, diacetate (salt); or H-Val-Val-LVA-Ile-Amp; FAB-MS: $[m + H]^+$ at 633;

(33) Ac-Asn-LVA-Ile-Amp; FAB-MS: $[m + H]^+$ at 591;

(34) L-Valinamide, N-acetyl-L-valyl-N-[2-hydroxy-5-methyl-1-(2-methylpropyl)-4-[[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]amino]carbonyl]hexyl]-, [1S-[1R*,2R*,4R*(1R*,2R*)]]-, monoacetate (salt); or Ac-Val-Val-LVA-Ile-Amp; FAB-MS: $[m + H]^+$ at 675;

(35) Nα-[(2S,4S,5S)-5-[N-[Nα-(Phenoxymethylcarbonyl)-L-histidyl]amino-4-hydroxy-2-isopropyl-7-methyl-1-oxooctyl]-N-[2-(2-pyridinylamino)ethyl]-L-isoleucinamide, acetic acid salt; or POA-His-LVA-Ile-$NH(CH_2)_2NH$-pyridine; FAB-MS: $[m + H]^+$ at 735;

(36) IVA-LVA-Ile-Amp; FAB-MS: $[m + H]^+$ at 519;

(37) N-[(2S,4S,5S)-5-[Nα-[Nα-(tert-Butoxycarbonyl)-O-methyl-L-tyrosyl]-L-histidyl]amino]-4-hydroxy-7-methyl-2-phenylmethyl-1-oxooctyl]-N-[(S)-2-hydroxypropyl]amine; or Boc-OMeTyr-His-LPA-$NH-CH_2-CH(CH_3)(OH)$; FAB-MS: $[m + H]^+$ at 751;

(38) Nα-[(2S,4S,5S)-5-[N-[Nα-(Phenoxymethylcarbonyl)-L-histidyl]amino]-4-hydroxy-2-isopropyl-7-methyl-1-oxooctyl]-N-(2,3-dihydroxypropyl)-L-isoleucinamide; or POA-His-LVA-Ile-$NH-CH_2-CH(OH)-CH_2OH$; FAB-MS: $[m + H]^+$ at 689;

(39) Nα-[(2S,4S,5S)-5-[N-[Nα-(Phenoxymethylcarbonyl)-L-histidyl]-amino-4-hydroxy-2-isopropyl-7-methyl-1-oxooctyl]-N-(2-hydroxypropyl)-L-isoleucinamide; or POA-His-LVA-Ile-$NH-CH_2-CH(CH_3)(OH)$; FAB-MS: $[m + H]^+$ at 673;

(40) Nα-[(2S,4S,5S)-5-[[Nα[(S)-1-Acetoxy-1-benzyl)methylcarbonyl]-L-histidyl]amino]-4-hydroxy-7-methyl-2-(1-methylethyl)-1-oxooctyl]-N-[2-pyridyl)ethyl]-L-isoleucinamide; or AcO-Phe-His-LVA-Ile-NH-$(CH_2)_2$-pyridine; FAB-MS: $[m + H]^+$ at 776;

(41) Nα-[(2S,4S,5S)-5-[[(S)-(1-Hydroxy-1-benzyl)methylcarbonyl]amino]-4-hydroxy)-7-methyl-2-(1-methylethyl)-1-oxooctyl]-N-(2-pyridinylmethyl)-L-isoleucinamide; or

HO-Phe-LVA-Ile-Amp; High Resolution MS: 583.3880;

(42) Nα-[(2S, 4S, 5S)-5-[N-[Nα-(1-Naphthalenyloxyacetyl)-L-histidyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide, pyridine N-oxide; or NOA-His-CVA-Ile-Amp-NO. HR FAB MS $[m+H]^+$ at m/z 812.4748;

(43) Nα-[(2S, 4S, 5S)-5-[N-[Nα-(P-toluenesulfonyl)-L-histidyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide or p-Tolunesulfonyl-His-CVA-Ile-Amp. HR FAB MS $[m + H]^+$ at m/z 766.4348;

(44) Nα-[(2S, 4S, 5S)-5-[N-[Nα-(1-Naphthalenyloxyacetyl)-L-histidyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide; or NOA-His-CVA-Ile-Amp. HR FAB MS $[m + H]^+$ at m/z 796.4794;

(45) Nα-[(2S, 4S, 5S)-5-[N-[Nα-(Phenoxymethylcarbonyl)-L-histidyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide, pyridine N-oxide; or POA-His-CVA-Ile-Amp-NO. HR FAB MS $[m + H]^+$ at m/z 762.4574;

(46) Nα-[(2S, 4S, 5S)-5-[N-[Nα-(p-Toluenesulfonyl)-L-histidyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide, pyridine N-oxide; or p-Toluenesulfonyl-His-CVA-Ile-Amp-NO. HR FAB MS $[m + H]^+$ at m/z 782.4238;

(47) Nε-[(2S, 4S, 5S)-5-[N-[Nα-(1-Naphthalenyloxyacetyl)-L-histidyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-L-lysine,trifluoroacectic acid salt; or NOA-His-CVA-L-lysine,trifluoroacetic acid salt. HR FAB MS $[m + H]^+$ at m/z 721.4309;

(48) N-[(2S, 4S, 5S)-5-[N-[Nα-(1-Naphthalenyloxyacetyl)-L-histidyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-[2-(2-pyridinylamino]ethyl]-amine; or NOA-His-CVA-NH-$(CH_2)_2$-NH-(2-pyridine) HR FAB MS $[m + H]^+$ at m/z 712.4195;

(49) N-[(2S, 4S, 5S)-5-[N-[Nα-(1-Naphthalenyloxyacetyl)-L-histidyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-[2-(2-pyridinylamino)]ethyl]amine,pyridine N-oxide; or NOA-His-CVA-NH$(CH_2)_2$-NH-(2-pyridine). HR FAB MS $[m + H]^+$ at m/z 728.4144;

(50) Nα-[(2S, 4S, 5S)-5-[N-[Nα-(1-Naphthalenyloxyacetyl) (2-pyridinyl)alanyl]-amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide; or NOA-His-CVA-Ile-Amp. HR FAB MS $[m + H]^+$ at m/z 807.4795;

(51) Nα-[(2S, 4S, 5S)-5-[N-[Nα-[(3-Pyridinyl)-methylcarbonyl]-L-histidyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide; or (3-pyridinyl)-methyl-carbonyl-His-CVA-Ile-Amp. HR FAB MS $[m + H]^+$ at m/z 731.4625;

(52) Nε-[Nα-[(2S, 4S, 5S)-5-[N-[Nα-(1-Naphthalenyloxyacetyl)-L-histidyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-L-isoleuncyl]-L-lysine, trifluoroacetic acid salt; or NOA-His-CVA-Ile-L-lysine, trifluoroacetic acid salt. HR FAB MS $[m+H]^+$ at m/z 834.5151;

(53) Nα-[(2S, 4S, 5S)-5-[N-[Nα-(1-Naphthalenyloxyacetyl)-L-histidyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-[2-(2-pyridinylamino)ethyl]-L-isoleucinamide; or NOA-His-CVA-Ile-NH-$(CH_2)_2$-NH-(2-pyridine). HR FAB MS $[m+H]^+$ at m/z 825.5040;

(54) 1H-Imidazole-4-propanamide,N-[2-hydroxy-5-methyl-1-(2-methylpropyl)-4-[[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]amino]carbonyl]hexyl]-α-[(2-hydroxy-1-oxo-3-phenylpropyl)amino]-,[1S-[1R*[R*(R*)],2R*,4R*(1R*,2R*)]]-, 2-hydroxy-1,2,3-propanetricarboxylate (1 2) (salt); or phenyl-$CH_2$-CH(OH)-C(O)-His-LVA-Ile-Amp. HR FAB MS $[m+H]^+$: 720.4456;

(55) 1H-Imidazole-4-propanamide,N-[2-hydroxy-4-[[[1-[[(2-hydroxy-2-phenylethyl)-amino]carbonyl]-2-methylbutyl]amino]carbonyl]-5-methyl-1-(2-methylpropyl)hexyl]-α-[(phenoxyacetyl)amino]-,monoacetate (salt); or POA-His-LVA-Ile-NH-$CH_2$-CH(OH)-phenyl. HR FAB MS $[m+H]^+$: 735.4444;

(56) L-α-Glutamine, N/u 2/d -[N-[[1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-N-[2-hydroxy-5-methyl-1-(2-methylpropyl)-4-[[[2-methyl-1-[[(2-pyridinylmethyl)amino]-carbonyl]butyl]amino]carbonyl]hexyl]-,[1S-[1R*,2R*4R*(1R*,2R*)]]-,monacetate (salt); or BOC-Phe-Glu-LVA-Ile-Amp. HR FAB MS $[m+H]^+$: 811.4988;

(57) Pentanoic acid, 5-[[1-(cyclohexylmethyl)-2-hydroxy-4-[[(2-hydroxy-propyl)amino]carbonyl]-5-methylhexyl]amino]-5-oxo-4-[(phenoxyacetyl)amino]-; or POA-Glu-CVA-NH-$CH_2CH(CH_3)(OH)$. HR FAB MS $[m+H]^+$: 630.3146;

(58) 1H-Imidazole-4-propanamide, N-[1-(cyclohexylmethyl)-2-hydroxy-4-[[(2-hydroxypropyl)amino]carbonyl]-5-methylhexyl]α-[(phenoxyacetyl)amino]-,monoacetate (salt); or POA-His-CVA-NH-$CH_2$-$CH(OH)(CH_3)$. HR FAB MS $[m+H]^+$: 600.3770;

(59) Pentanoic acid, 5-[[1-(cyclohexylmethyl)-2-hydroxy-5-methyl-4-[[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]amino]carbonyl]hexyl]amino]-4-[(1H-indol-2-ylcarbonyl)amino]-5-oxo-,[1S-[1R*(R*),2R*,4R*(1R*,2R*)]]-; or 1H-indol-2-yl-carbonyl-Glu-CVA-Ile-Amp. HR FAB MS $[m+H]^+$: 747.4437;

(60) L-.alpha.-Glutamine, N-[1-(cyclohexylmethyl)-2-hydroxy-5-methyl-4-[[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]amino]carbonyl]hexyl]-N/u 2/d-L-phenyl-alanyl-, [1S-[1R*,2R*,4R*(1R*,2R*)]]-, bis(trifluoracetate) (salt); or Phe-Glu-CVA-Ile-Amp. HR FAB MS $[m+H]^+$: 751.4756;

(61) 2-Pyridineacetamide, N-[2-[[2-hydroxy-5-methyl-1-(2-methylpropyl)-4-[[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]amino]carbonyl]hexyl]amino]-1-(1H-imidazol-4-ylmethyl)-2-oxoethyl]-[1S-[1R*(R*),2R*,4R*(1R*,2R*)]]-; or (2-Pyridyl)acetyl-His-LVA-Ile-Amp;

(62) 4-Pyridineacetamide, N-[2-[[2-hydroxy-5-methyl-1-(2-methylpropyl)-4-[[[2methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]amino]carbonyl]hexyl]amino]-1-(1H-

imidazol-4-ylmethyl)-2-oxoethyl]-[1S-[1R*(R*),2R*,4R*(1R*,2R*)]]-; or (4-Pyridyl)acetyl-His-LVA-Ile-Amp;

(63) L-Histidinamide, N-[(1,1-dimethylethoxy)carbonyl]-3-(2-pyridinyl)alanyl-N-[2-hydroxy-5-methyl-1-(2-methylpropyl)-4-[[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]amino]carbonyl]hexyl]-,[1S-[1R*[R*(E)],2R*,4R*(1R*,2R*)]]-; or BOC-2-Py-Ala-His-LVA-Ile-Amp. HR FAB MS [m +H]$^+$: 820.5112;

(64) L-Histidinamide, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-[4-[[[2-[(2,6-diamino-4-pyrimidinyl)amino]ethyl]amino]carbonyl]-2-hydroxy-5-methyl-1-(2-methylpropyl)hexyl]-,[1S-(1R*,2R*,4R*)]-; or BOC-Phe-His-LVA-(2,6-diamino-4-pyrimedinyl)amino-ethylamino. HR FAB MS [m + H]$^+$: 766.4727;

(65) L-.alpha.-Asparagine, N/u 2/d-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-N-[2-hydroxy-5-methyl-1-(2-methylpropyl)-4-[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]amino]carbonyl]hexyl]-,[1S-[1R*,2R*,4R*(1R*,2R*)]]-,monoacetate (salt); or BOC-Phe-Asp-LVA-Ile-Amp. HR FAB MS [m +H]$^+$: 797.4857;

(66) 1H-Indole-2-carboxamide, N-[2-([2-hydroxy-5-methyl-1-(2-methylpropyl)-4-[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]carbonyl]hexyl]amino]-1-(1H-imidazol-4-ylmethyl)-2-oxoethyl]-,[1S-[1R*(R*),2R*,4R*(1R*,2R*)]]-; or N-(Indolyl-2-carbonyl)-His-LVA-Ile-Amp;

(67) L-.alpha.-Glutamine, N-[1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-N0[1-(cyclohexylmethyl)-2-hydroxy-5-methyl-4-[[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]amino]carbonyl]hexyl]]-,[1S-[1R*,2R*,4R*(1R*,2R*)]]-, monoacetate (salt); or BOC-Phe-Glu-CVA-Ile-Amp. HR FAB MS [m + H]$^+$: 851.5297;

(68) 2,5,11,14-Tetraazapentadecanoic acid, 7-hydroxy-3-(1H-imidazol-4-ylmethyl)-9-(1-methylethyl)-12-(1-methylpropyl)-6-(2-methylpropyl)-4,10,13-trioxo-15-(2-pyridinyl)-,4-pyridinylmethyl ester, [3S-[3R*,6R*,7R*,9R*,12R*(R*)]]-; or Ioc-His-LVA-Ile-Amp;

(69) L-Histidinamide, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-[3,3-difluoro-2-hydroxy-4-[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]amino]-4-oxo-1-(phenylmethyl)butyl]-; or $CH_3$-C(O)-O-CH(benzyl)-C(O)-His-LVA-Ile-Amp. HR FAB MS [m + H]$^+$: 762.4521;

(70) 1H-Imidazole-4-propanamide, N-[2-hydroxy-5-methyl-1-(2-methylpropyl)-4-[[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]amino]carbonyl]hexyl]-$\alpha$-[(1-oxo-3-phenoxypropyl)amino]-,[1S-[1R*(R*),2R*,4R*(1R*,2R*)]]-; or Phenoxy-propionyl-His-LVA-Ile-Amp;

(71) 1H-Imidazole-4-propanamide,N-[2-hydroxy-5-methyl-1-(2-methylpropyl)-4-[[[2-methyl-1-[[[(2-pyridinylmethyl)amino[carbonyl[butyl[amino[carbonyl[hexyl]-$\alpha$-[(1-oxo-3phenyl-2-propenyl)amino]-,[1S-[1R*[R*(E)],2R*,4R*(1R*,2R*)]]-; or phenyl-CH=CH-C(O)-His-

LVA-Ile-Amp. HR FAB MS $[m + H]^+$: 702.4343;

(72) 1H-Imidazole-4-propanamide,N-[2-hydroxy-5-methyl-1-(2-methylpropyl)-4-[[[2-methyl-1-[[[(2-pyridinylmethyl)amino[carbonyl][butyl]amino[carbonyl[hexyl]-α-[(1-oxo-4-phenyl-3-butenyl)amino]-,[1S-[1R*[R*(E)],2R*,4R*(1R*,2R*)]]-; or phenyl-CH=CH-$CH_2$-C(O)-His-LVA-Ile-Amp. HR FAB MS $[m + H]^+$: 716.4474;

(73) 2,5,11,14-Tetraazapentadecanoic acid, 7-hydroxy-3-(1H-imidazol-4-ylmethyl)-9-(1-methylethyl)-12-(1-methylpropyl)-6-(2-methylpropyl)-4,10,13-trioxo-15-(2-pyridinyl)-,3-phenyl-2-propenyl ester, [3S-[1(E),3R*,6R*,7R*,9R*,12R*(R*)]]-; or phenyl-CH=CH-$CH_2$-O-C(O)-His-LVA-Ile-Amp. HR FAB MS $[m + H]^+$: 732.4463;

(74) 1H-Imidazole-4-propanamide,N-[2-hydroxy-5-methyl-1-(2-methylpropyl)-4-[[[2-methyl-1-[[(2-pyridinylmethyl)amino]carbonyl]butyl]amino]carbonyl]hexyl]-α-[[(2-phenylethenyl)sulfonyl]amino]-,[1S-[1R*[R*(E)],2R*,4R*(1R*,2R*)]]-; or phenyl -$(CH_2)_2$-$SO_2$-His-LVA-Ile-Amp. HR FAB MS $[m + H]^+$: 738.4061;

(75) N-tert-Butyloxycarbonyl-L-phenylalanyl-L-histidyl-5S-amino-3R,4R-dihydroxy-2R-isopropyl-7-methyl-octanoyl-2S-methylbutylamide; or BOC-Phe-His-LVA-Mba. FAB-MS (found): 701.4634;

(76) Hydroxyacetyl-L-histidyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or (HO)Ac-His-CVA-Ile-Amp. FAB-MS (found): 686.4244;

(77) L-Glycyl-L-histidyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or Gly-His-CVA-Ile-Amp. FAB-MS (found): 685.4382;

(78) Hydroxyacetyl-L-histidyl-5S-amino-2R-benzyl-6-cyclohexyl-3R,4R-dihydroxy-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or (HO)Ac-His-CPD-Ile-Amp. FAB-MS (found): 734.4248;

(79) Hydroxyacetyl-L-histidyl-5S-amino-2R-benzyl-6-cyclohexyl-3R,4R-dihydroxy-hexanoyl-L-isoleucyl-2-pyridylmethylamide, N-oxide; or (HO)Ac-His-CPD-Ile-Amp. FAB-MS (found): 750.4202;

(80) Phenoxyacetyl-L-histidyl-5S-amino-2R-benzyl-6-cyclohexyl-3R,4R-dihydroxy-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or POA-His-CPD-Ile-Amp. FAB-MS (found): 810.4557;

(81) L-Glycyl-L-histidyl-5S-amino-2R-benzyl-6-cyclohexyl-3R,4R-dihydroxy-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or Gly-His-CPD-Ile-Amp. FAB-MS (found): 733.4409;

(82) Phenoxyacetyl-L-histidyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or POA-His-CVA-Ile-Amp. FAB-MS

(found): 762.4574;

(83) 1-Naphtoxyacetyl-L-histidyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isobutyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or NOA-His-CLD-Ile-Amp. FAB-MS (found): 826;

(84) 1-Naphthoxyacetyl-L-histidyl-5S-amino-6-cyclohexyl-2R-cyclohexylmethyl-3R,4R-dihydroxy-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or NOA-His-CCD-Ile-Amp. FAB-MS (found): 866.5189;

(85) 1-Naphthoxyacetyl-L-histidyl-5S-amino-2R-benzyl-3R,4R-dihydroxy-6-phenyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or NOA-His-PPD-Ile-Amp. FAB-MS (found): 854:4230;

(86) 1-Naphthoxyacetyl-L-histidyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-pyridinylamino-ethylamide; or NOA-His-CVD-Ile-Apr. FAB-MS (found): 841.4964;

(87) 1-Naphthoxyacetyl-L-histidyl-5S-amino-6-cyclohexyl-2S-cyclohexylmethyl-3R,4R-dihydroxy-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or NOA-His-CcD-Ile-Amp. FAB-MS (found): 866.5194;

(88) 1-Naphthoxyacetyl-L-histidyl-5S-amino-3S-4S-dihydroxy-2S-isobutyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide; or NOA-His-LlD-Ile-Amp. FAB-MS (found): 786.4540;

(89) 5-Quinolinylhydroxyacetyl-L-histidyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or Qoa(b)-His-CVA-Ile-Amp. FAB-MS (found): 797;

(90) 4-Quinolinylhydroxyacetyl-L-histidyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or Qoa(a)-His-CVA-Ile-Amp. FAB-MS (found): 797;

(91) 1-Naphthoxyacetyl-L-histidyl-5S-amino-3R-4R-dihydroxy-2S-isobutyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide; or NOA-His-LLd-Ile-Amp. FAB-MS (found): 786.4579;

(92) 1-Naphthoxyacetyl-L-histidyl-5S-amino-3S-4R-dihydroxy-2S-isobutyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide; or NOA-His-LLd-Ile-Amp. FAB-MS (found): 786.4556;

(93) 1-Naphthoxyacetyl-L-histidyl-5S-amino-3R-4R-dihydroxy-2R-isobutyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide; or NOA-His-LLD-Ile-Amp. FAB-MS (found): 786.4540;

(94) 2-Quinolinylcarbonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-pyridinylamino-ethylamide; or Qc-Asn-CVD-Ile-Apr. FAB-MS (found):

789.4670;

(95) N-tert-Butyloxycarbonyl-L-alanyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or Boc-Ala-CVA-Ile-Amp. FAB-MS [m + H]$^+$: 546;

(96) N-tert-Butyloxycarbonyl-L-histidyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or BOC-His-CVA-Ile-Amp. FAB-MS [m + H]$^+$: 712;

(97) Quinolinyl-2-carbonyl-L-histidyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or QC-His-CVA-Ile-Amp. FAB-MS [m + H]$^+$: 768;

(98) Quinolinyl-2-carbonyl-L-asparaginyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or QC-Asn-CVA-Ile-Amp. FAB-MS [m +H]$^+$: 744;

(99) Benzyloxycarbonyl-L-alanyl-L-alanyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or CBZ-Ala-Ala-CVA-Ile-Amp. FAB-MS [m +H]$^+$: 751;

(100) 1-Naphthalenyloxyacetyl-L-histidyl-5S-amine-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucylamide; or Noa-His-CVA-Ile-$NH_2$. FAB-MS [m + H]$^+$: 705;

(101) POA-His-CVA-NH-$(CH_2)_4$-CH(CONH)($NH_2$). FAB-MS [m + H]$^+$: 671;

(102) L-Asparaginamide, 1-(naphthoxy)acetyl-N-[2-hydroxy-5-methyl-1-(2-methylpropyl)-4-[[[2-methyl-1-[[[2-(N-oxido)pyridinylmethyl]amino]carbonyl]butyl]amino]carbonyl]hexyl]-N-alpha-methyl-, [1S-[1R*,2R*,4R*(1R*,2R*)]]-; or NOA-Asp-CVA-Ile-Amp. Mass Spectrum: No exact mass obtained because of weak M + H$^+$ ion. Other ions at m/z 665,535,348,354,236,222,157,126,109,86;

(103) L-Asparaginamide, [5-(triethyleneglycol monomethyl ether)naphthoxy]acetyl-N-[2-hydroxy-5-methyl-1-(2-methylpropyl)-4-[[[2-methyl-1-[[[2-(N-oxido)pyridinyl-methyl]amino]carbonyl]butyl]amino]carbonyl]hexyl]-N-alpha-methyl-, [1S-[1R*,2R*,4R*(1R*,2R*)]]; or 5-[$CH_3(OCH_2CH_2)_3O$]-1-Noa-Asn-CVA-Ile-Amp;

(104) L-Asparaginamide, [4-(triethyleneglycol monomethyl ether)naphthoxy]acetyl-N-[2-hydroxy-5-methyl-1-(2-methylpropyl)-4-[[[2-methyl-1-[[[2-(N-oxido)pyridinylmethyl]amino]carbonyl]butyl]amino]carbonyl]hexyl]-N-alpha-methyl-, [1S-[1R*,2R*,4R*(1R*,2R*)]]; or 4-[$CH_3(OCH_2CH_2)_3O$]-1-Noa-Asn-CVA-Ile-Amp;

(105) L-Glycyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-=L-isoleucyl-2-pyridylmethylamide-; or Gly-CVD-Ile-Amp. FAB-MS (found): 548.3844; and

(106) L-Glycyl-5S-amino-2R-benzyl-6-cyclohexyl-3R,4R-dihy-droxy-hexanoylL-isoleucyl-2-pyridyl-methylamide; or Gly-CPD-Ile-Amp. FAB-MS (found): 596.3835.

The following describes the general procedures that are used in the preparations and examples below:

Silica gel used for chromatography is obtained from E. Merch A.G., Darmstadt, Germany. Silica gel GF, 250 micron slides obtained from Analtech, Inc., Newark, DE are used for TLC. Celite is a filter aid manufactured by Johns-Manville, New York. FAB mass spectra are obtained on a Varian CH5 mass spectrometer, IR spectra on a Digilab FTS15E and NMR spectra on a Brucker AM300. Melting points are taken in capillary tubes and are uncorrected.

Procedure A - Boc group removal:

A 5% solution of the Boc protected amine in an equal volume of methylene chloride and trifluoracetic acid is allowed to stir at room temp (temperature) for 1-3h and then concentrated *in vacuo*. A solution of the residue in methylene chloride is washed once with aqueous sodium bicarbonate. The aqueous wash is backwashed twice with methylene chloride. The combined organic fractions are dried over magnesium sulfate and concentrated *in vacuo*. The residue is then used as is in the next step without further purification.

Procedure B - Coupling an acid to an amine using diethyl cyanophosphonate (DEPC):

To a nitrogen covered 0.04 molar solution of the free amine in methylene chloride is added 1.25 equivalents of the acid followed by 1.25 equivalents of triethylamine and 1.4 equivalents of diethyl cyanophosphonate (DEPC). The solution is allowed to stir at room temperature for 2-24 hr, diluted with methylene chloride, and washed once with aqueous sodium bicarbonate. The aqueous fraction is backwashed twice with methylene chloride. The organic fractions are combined, dried over magnesium sulfate, and concentrated *in vacuo*. The residue is then chromatographed over silica gel to yield the coupled product.

Procedure C - Coupling an amine to an acid using diethyl cyanophosphonate (DEPC):

To a nitrogen covered 0.04 molar solution of the acid in methylene chloride is added 1.25 equivalents of the amine followed by 1.25 equivalents of triethylamine and 1.4 equivalents of diethyl cyanophosphonate. The solution is allowed to stir at room temperature for 2-24 hr, diluted with methylene chloride, and washed once with aqueous sodium bicarbonate. The aqueous fraction is backwashed twice with methylene chloride. The organic fractions are combined, dried over magnesium sulfate, and concentrated *in vacuo*. The residue is then chromatographed over silica gel to yield the coupled product.

Procedure D - Catalytic proton transfer hydrogenolysis:

To a 0.01 molar suspension of the protected amine in N,N-dimethylformamide, under nitrogen is added 10% Pd/C catalyst and 11 equivalents of ammonium formate. The suspension is stirred at room temperature overnight, warmed in a warm water bath for 15 min and filtered through Celite. The solid is washed with warm N,N-dimethylformamide and the

filtrate is concentrated *in vacuo*. The residue is dissolved in acetic acid, diluted with water and freeze dried to give product as the acetic acid salt.

Procedure E - Preparative HPLC:

To determine conditions for a separation on our preparative reverse phase HPLC column we first develop suitable conditions for the separation on an analytical column with the same packing. Using the parameters from this analytical separation and the equation Q in the Structure Chart below we are then able to calculate the maximum percent of solvent B for the gradient phase of the preparative separation.

In equation Q, e(%) is the maximum percent of solvent B for the gradient phase of the preparative separation; $t_o$ is the retention time (min) for unretained materials on the analytical column and t is the longest retention time (min) for the products of interest. The analytical separation is usually carried out with an isocratic elution phase followed by a linear gradient from the isocratic solvent concentration to 100% solvent B. For this mode of operation x represents the duration (min) of the isocratic portion of the separation and y represents the duration (min) of the gradient portion. A (%) and B(%) represent the percent of solvents A and B in the initial isocratic solvent mixture.

In a typical example.

Solvent A - 90% $H_2O$:0.1% TFA:$CH_3CN$

Solvent B - 30% $H_2O$:0.1% TFA:$CH_3CN$

Analytical conditions:

Column: Whatman Partisil ODS-3, 10 $\mu$, 250 x 4.6 mm

Isocratic solvent: 83% A: 17% B

Isocratic duration (x): 2 min

Linear gradient: 83% A: 17% B to 100% B

Gradient duration (y): 20 min

Flow rate: 2 ml/min

$t_o$ = 1.2 min

t = 12.63 min

Result: e(%) = 51 (See equation U in the Structure Chart below.)

Preparative conditions:

Column: Whatman Partisil ODS-3, 10 $\mu$, 500 x 22 mm

Isocratic solvent: 83% A: 17% B

Isocratic duration: 15 min

Linear gradient: 83% A: 17% B to 49% A: 51% B

Gradient duration: 90 min

Flow rate: 3 ml/min

Using these conditions for the preparative column a 0.0285 g sample (injected onto the column in 0.7 ml of solvent B) is eluted in 138 min and is contained in 31.5 ml of eluant.

Procedure F-Trifluoroacetic acid silyl ether cleavage.

To a nitrogen covered 0.14 molar solution of the silyl ether in methylene chloride in an ice bath, a volume of trifluoroacetic acid equal to the volume of methylene chloride is added dropwise. The ice bath is removed and after stirring for 2.5-5.0 hr. (TLC monitored) the solution is concentrated *in vacuo*. A solution of the residue in methylene chloride is washed once with aqueous sodium bicarbonate, dried over magnesium sulfate, and concentrated in vacuo. The residue is then chromatographed over silica gel to yield product.

PREPARATION 107 $N_{\alpha}$-[2S,4S,5S)-5-(tert-Butoxy carbonylamino)-4-(tert-butyldimethylsilyloxy)-6-cyclohexyl-2-isopropyl-1-oxohexyl]-L-isoleucine or (Boc(OTBDMS)CVA Ile].

A. To a nitrogen covered solution of 0.51 g of L-isoleucine, benzyl ester, P-toluenesulfonic acid salt in 24 ml of methylene chloride is added 0.34 ml of triethylamine. After stirring at room temperature for 10 min, there is added 0.5 g of [2S,4S,5S)-5-(tert-butoxy carbonylamino)-4-(tert-butyldimethylsilyloxy)-6-cyclohexyl-2-isopropylhexanoic acid or Boc(OTBDMS) CVA (The Preparation of this compound is in U.S. Patent application, Serial No. 07/566,340 filed August 2, 1990, Preparation 48, page 100) and 0.22 ml of diethyl cyano-phosphonate. After stirring for an additional 19 hr at room temperature, the reaction mixture is diluted with methylene chloride, washed with aqueous sodium bicarbonate, dried over magnesium sulfate and concentrated in vacuo. The residue is chromatographed over 175 ml of silica gel (elution with 10% ethyl acetate: hexane) to yield 0.633 g of the coupled product (Boc (OTBDMS) CVAIleOBz).

The structure is supported by NMR and a FAB mass spectrum. Found: $[m^{\cdot}+H]^{+}$ at m/z 689.

B. A mixture of 0.633 g of the benzyl ester of Part A and 0.2 g of 10% Pd/C catalyst in 25 mL of absolute ethanol is stirred vigorously under hydrogen at atmospheric pressure. After 50 min the catalyst is removed by filtration through Celite and the filtrate is concentrated in vacuo to yield 0.507 g of the titled product.

Physical characteristics of the titled product are as follows:

The structure is supported by NMR and a FAB mass spectrum. Found: $[m^{\cdot}+H]^{+}$ at m/z 599.

PREPARATION 108 $N_{\alpha}$-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-[2-(2-pyridinylamino)ethyl]-L-isoleucinamide or 2-Pyridinylcarbonyl-CVA-Ile-NH-$(CH_2)_2$-NH-2-pyridinyl.

A. By the coupling Procedure C, 0.50 g of the peptide of Preparation 107 is coupled with 2-(2-pyridylamino)ethylamine (prepared as described in Preparation 109 below) and chromatographed over silica gel (3% methanol: 0.3% ammonium hydroxide: methylene chloride) to yield 0.4798 g of coupled product Boc(OTBDMS)CVAIleNH-$(CH_2)_2$-NH-2-pyridinyl.

The structure is supported by NMR and a FAB mass spectrum Found: $[m^{\cdot}+H]^+$ at m/z 718.

B. By the general Procedure A for Boc group removal, 0.15 g of the Boc amine of Part A yields 0.1299 g of the amine free base. The amine is then coupled (coupling Procedure B) to picolinic acid and chromatographed over silica gel (3% methanol: 0.3% ammonium hydroxide: methylene chloride) to yield 0.1226 g of coupled product, 2-pyridinylcarbonyl(OTBDMS)CVA-Ile-NH-$(CH_2)_2$-NH-2-pyridinyl.

The structure is supported by NMR and a FAB mass spectrum. Found: $[m^{\cdot}+H]^+$ at m/z 723.

C. To a nitrogen covered, ice bath cooled solution of 0.1226 g of the silyl ether of Part B in 1.2 ml of methylene chloride is added dropwise 1.2 ml of trifluoroacetic acid. The ice bath is removed and after stirring at room temperature for 3 hr, the solution is concentrated in vacuo. A solution of the residue in methylene chloride is washed once with aqueous sodium bicarbonate, dried over magnesium sulfate and concentrated in vacuo. The residue is chromatographed over silica gel (3.5% methanol: 0.35% ammonium hydroxide: methylene chloride) to yield 0.0802 g of the titled product.

Physical characteristics of the titled product are as follows:

The structure is supported by a high resolution FAB mass spectrum. Found: $[m^{\cdot}+H]^+$ at m/z 609. Measured = 609.4116.

CV-1 Assay (% Inhibition): 100% at 10 $\mu$M; 82% 1 $\mu$M; 18% at 0.3 $\mu$M; 1% at 0.1 $\mu$M.

PREPARATION 109 2-(2-Pyridylamino)ethylamine.

To 73 ml of nitrogen covered ethylenediamine cooled to just above the freezing point with the intermittent use of an ice bath is added 4.3 ml of 2-chloropyridine over 15 min. After stirring in the cold for an additional 25 min, the ice bath is removed and the solution is stirred at room temperature for 24 hr and then heated at 85° for 24 hr and at 125°-130° for 48 hr. After cooling, the reaction mixture is concentrated in vacuo. The residue is treated with water and extracted 3 times with ethyl acetate. The combined extracts are washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue is chromatographed over 300 ml of silica gel. Elution is carried out first using 3% methanol:methylene chloride containing 0.3% ammonium hydroxide collecting 12 ml fractions. At fraction 137, the solvent is changed

to 5% methanol:methylene chloride containing 0.5% ammonium hydroxide and then at fraction 277 the solvent is changed to 30% methanol:methylene chloride containing 0.5% ammonium hydroxide and 21 ml fractions are then collected. Fractions 366-420 are combined to yield 1.52 g of the titled product.

Physical characteristics of the title product are as follows:

The structure is supported by NMR, IR, and mass spectra.

EXAMPLE 1 $N_{\alpha}$-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-(O-phosphoryl)-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide, hydrochloric acid salt or 2-Pyridinylcarbonyl-($OPO_3H_2$)CVA-Ile-Amp.

According to the procedure described in Example 2, below the product from Preparation 108 is allowed to react first with di-tert-butyl N,N-diethylphorphoramidite and 1H-tetrazole and then with m-chloroperoxybenzoic acid to give $N_{\alpha}$-[(2S,4S,5S)-5-[N-(2-pyridinyl-carbonyl)amino]-6-cyclohexyl-4-(O-di-tert-butylphosphoryl)-2-isopropyl-1-oxohexyl]-N-[2-(2-pyridinylamino)ethyl]-L-isoleucinamide which is treated with concentrated hydrochloride acid to give the titled product.

PREPARATION 110 $N_{\alpha}$-[(2S,4S,5S)-5-(tert-Butoxy carbonylamino)-4-(tert-butyldimethyl-silyloxy)-6-cyclohexyl-2-isopropyl-1-oxohexyl]-N-(2-pyridinyl)methyl]-L-isoleucinamide or Boc (OTBDMS) CVA Ile Amp.

By coupling Procedure C, 0.507 g of the peptide of Preparation 107 is coupled with 2-(aminomethyl)pyridine and chromatographed over 150 ml of silica gel (elution with 3% methanol:methylene chloride containing 0.3% ammonium hydroxide) to yield 0.48 g of the titled product.

Physical characteristics of the titled product are as follows:

The structure is supported by NMR.

Mass spectrum Found: $[m^{\cdot}]^{+}$ at m/z 688.

PREPARATION 111 $N_{\alpha}$-[(2S,4S,5S)-5-Amino-4-(tert-butyldimethylsilyloxy)-6-cyclohexyl-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide or (OTBDMS) CVA-Ile-Amp.

By the general Procedure A for Boc group removal, 1.0 g of the Boc protected amine of Preparation 110 yields 0.968 g of the amine free base.

PREPARATION 112 $N_{\alpha}$-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucin-amide or 2-Pyridinylcarbonyl-CVA-Ile-Amp.

A. By the general coupling Procedure B, 0.10 g of the amine free base of Preparation 111 is coupled with picolinic acid and chromatographed over silica gel (2.5% methanol: 0.25% ammonium hydroxide:methylene chloride) to yield 0.077 g of the product 2-

pyridinylcarbonyl-(OTBDMS) CVA-Ile-Amp.

The structure is supported by NMR.

FAB mass spectrum, Found: $[m^{\cdot}+H]^+$ at m/z 694.

B. By the general procedure F, 0.0770 g of the silyl ether of Part A is allowed to react and is then chromatographed over silica gel (3.5% methanol: 0.35% ammonium hydroxide:methylene chloride) to yield 0.0448 g of the titled product.

Physical characteristics of the titled product are as follows:

The structure is supported by a high resolution FAB mass spectrum Found: $[m+H]^+$ at m/z 580. Measured = 580.3858.

CV-1 Assay (% Inhibition): 85% at 10 $\mu$M; 84% at 10 $\mu$M; 65% at 3 $\mu$M; 40% at 1 $\mu$M; 16% at 0.3 $\mu$M; 11% at 0.1 $\mu$M.

HIV-1 Protease ($K_I$, nM): 30.

EXAMPLE 2 $N_\alpha$-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-(O-phosphoryl)-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide trifluoroacetic acid salt or 2-Pyridinylcarbonyl-($OPO_3H_2$)CVA-Ile-Amp.

To a stirred solution of the product from Preparation 112 (0.100g) in tetrahydroforuan (5 ml), under nitrogen, is added 1H-tetrazole (0.073 g) and di-tert-butyl N,N-diethylphosphoramidite (0.14 ml). This mixture is kept at ambient temperature (25°) for 52 hr, cooled in an ice bath and treated during 2 min with a solution of 85% m-chloroperoxybenzoic acid (0.105g) in methylene chloride (2 ml). It is kept in the ice bath for an additional 20 min. and then treated with a 10% aqueous solution of sodium sulfite (4.2 ml). The layers are separated and the aqueous layer is extracted with methylene chloride. The organic layers are combined, dried over magnesium sulfate and concentrated in vacuo. The residue is chromatographed over silica gel (3.75% methanol:0.38% ammonium hydroxide:methylene chloride) to yield 0.086 g of $N_\alpha$-[(2S,4S,5S)-5-[N-(2-pyridinylcarbonyl)amino]-6-cyclohexyl-4-(O-di-tert-butyl phosphoryl)-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide. A solution of this product in tetrahydrofuran (0.9 ml), under nitrogen, is treated, dropwise with 0.44 ml of concentrated hydrochloric acid. It is stirred for 1 hr at ambient temperature and then concentrated in vacuo to one half of its original volume. The residue is freeze dried to give 0.087 g of the titled product as its hydrochloric acid salt. A portion of this material (0.055 g) is chromatographed over a 22 x 500 mm Partisil -10 ODS-3 preparative reverse phase HPLC column (see general procedure E). Elution is isocratic at 83% solvent A:17% solvent B for 15 min followed by a linear gradient to 40% solvent A:60% solvent B during 90 min. The flow rate is 3 ml per min. The yield of the titled product is 0.0171 g.

Physical characteristic of the title product are as follows:

FAB mass spectrum: found $[M+H]^+$ at m/z 660, measured 660.3521.

CV-1 Assay (%Inhibition): 49% at 10$\mu$M; 40% at 1$\mu$M.

PREPARATION 113 $N_{\alpha}$-[(2S,4S,5S)-5-[N-[2-(3-Pyridinyl)ethenylcarbonyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide or 3-Pyridinyl-CH=CH-C(O)-CVA-Ile-Amp.

CV-1 Assay (% Inhibition): 57% at 1 $\mu$M; 68% at 1 $\mu$M.

A. By the general coupling Procedure B, 0.20 g of the amine free base of Preparation 111 is coupled with 3-(3-pyridyl)acrylic acid and chromatographed over silica gel (4% methanol: 0.4% ammonium hydroxide: methylene chloride) to yield 0.175 g of the product 3-pyridinyl-CH=CH-C(O)-(OTBDMS) CVA-Ile-Amp.

The structure is supported by NMR.

FAB mass spectrum Found: $[M^{\cdot}+H]^{+}$ at m/z 720.

B. By the general Procedure F for silyl ether cleavage, 0.171 g of the silyl ether of Part A is allowed to react and is then chromatographed over silica gel (5% methanol: 0.5% ammonium hydroxide:methylene chloride) to yield 0.122 g of the titled product as a crystalline solid.

Physical characteristics of the titled product are as follows:

M. p: 216-220°C.

The structure is supported by a high resolution FAB mass spectrum. Found: $[m^{\cdot}+H]^{+}$ at m/z 606. Measured = 606.4025.

HR FAB MS $[m + H]^{+}$ at m/z 606.4025.

EXAMPLE 3 $N_{\alpha}$-[(2S,4S,5S)-5-[N-[2-(3-Pyridinyl)ethenylcarbonyl]amino]-6-cyclohexyl-4-(0-phosphoryl)-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide, hydrochloric acid salt or 3-Pyridinyl-CH=CH-C(O)-($OPO_3H_2$)CVA-Ile-Amp.

According to the procedure described in Example 2 the product from Preparation 113 is allowed to react first with di-tert-butyl N,N-diethylphosphoramidite and 1H-tetrazole and then with m-chloroperoxybenzoic acid to give $N_{\alpha}$-[(2S,4S,5S)-5-[N-[2-(3-pryidinyl) ethenylcarbonyl]amino]-6-cyclohexyl-4-(O-di-tert-butylphosphoryl)-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide which is treated with concentrated hydrochloric acid to give the titled product.

PREPARATION 114 $N_{\alpha}$-[(2S,4S,5S)-5-[N-[2-(3-Pyridinyl)ethylcarbonyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide or 3-Pyridinyl-$(CH_2)_2$-C(O)-CVA-Ile-Amp.

To a nitrogen covered, partial solution of 0.0653 g of the alkene of Preparation 113 in 4 ml of absolute ethanol is added 0.02 g of 10% Pd/C catalyst. The mixture is placed on an atmospheric hydrogenator with vigorous stirring. After 22.5 hr the mixture is removed and filtered through Celite to remove the catalyst. The filtrate is concentrated in vacuo. The

residue is chromatographed over silica gel (5% methanol: 0.5% ammonium hydroxide: methylene chloride) to yield 0.0577 g of the titled product.

Physical characteristics of the titled product are as follows:

The structure is supported by a high resolution FAB mass spectrum. Found $[M^{\cdot}+H]^+$ at m/z 608. Measured = 608.4166.

CV-1 Assay (% Inhibition): 18% at 1 $\mu$M; 50% at 1 $\mu$M.

EXAMPLE 4 $N_\alpha$-[(2S,4S,5S)-5-[N-[2-(3-Pyridinyl)ethylcarbonyl]amino]-6-cyclohexyl-4-(0-phosphoryl)-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide,hydrochloric acid salt or 3-Pyridinyl-$(CH_2)_2$-C(O)-$(OPO_3H_2)$CVA-Ile-Amp.

According to the procedure described in Example 2, the product from Preparation 114 is allowed to react first with di-tert-butyl N,N-diethylphosphoramidite and 1H-tetrazole and then with m-chloroperoxybenzoic acid to give $N_\alpha$-[(2S,4S,5S)-5-[N-[2-(3-pyridinyl)-ethylcarbonyl]amino]-6-cyclohexyl-4-(0-di-tert-butyl phosphoryl)-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide which is treated with concentrated hydrochloric acid to give the titled product.

PREPARATION 115 2-[(2,4-Diaminopyrimidin-6-yl]amino]ethylamine.

A nitrogen covered mixture of 5.0 g of 4-chloro-2, 6-diaminopyrimidine in 60 ml of ethylenediamine is heated at 85° for 24 hr at 130° for 22 hr and then allowed to stand at room temperature for 24 h. The residual ethylenediamine is removed by distillation and the pot residue is slurried in 1:1 methanol:methylene chloride.

The suspended solid (4.855 g) is collected on a filter and dried under vacuum. A portion (0.5 g) of this solid residue is chromatographed over a 50 ml silica gel column (elution with 50% methanol:methylene chloride containing 1% ammonium hydroxide) and 4.8 ml fractions are collected. Fractions 47-110 are combined to yield 0.323 g of the title product.

Physical characteristics of the titled product are as follows:

The structure is supported by mass spectrum, found $M^+$ at m/z 168.

PREPARATION 116 $N_\alpha$-[(2S, 4S, 5S)-5-[N-[$N_\alpha$-(1-Naphthalenyloxyacetyl)-L-histidyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl-L-isoleucinamide or NOA-His-CVA-Ile-Amp.

A. By the general Procedure A for Boc group removal, 0.20 g of the Boc amine of Preparation 110 yields 0.191 g of the free amine. The amine is then coupled (coupling Procedure B) with Boc-im-tosyl histidine and chromatographed over 150 ml of silica gel (elution with 3% methanol:methylene chloride containing 0.3% ammonium hydroxide) to yield 0.241 g of the coupled product, Boc (Tos) His (OTBDMS)CVA Ile Amp. The structure was supported by NMR and a FAB mass spectrum. Found: $[m+H]^+$ at mz 980.

B. By the general Procedure A for Boc group removal, 0.206 g of the Boc amino silyl ether of Part A yielded 0.1716 g of the amine free base having the silyl ether cleaved. A portion 0.104 g of the free base is coupled (coupling Procedure B) with 1-naphthalenyloxyacetic acid and chromatographed over silica gel (3.5% methanol:0.35%ammonium hydroxide:methylene chloride) to yield 0.102 g of couled product, NOA(Tos) His CVA Ile Amp. The structure is supported by a FAB mass spectrum. Found: $[m+H]^+$ at m/z 950.

C. To a nitrogen covered solution of 0.030 g of the tosyl protected peptide of Part B in 2.6 ml of dimethylformamide is added 0.043 g of 1-hydroxybenzotriazole. After stirring at room temperature for 18.5 hours the mixture is concentrated in vacuo. The residue is chromatographed over silica gel to yield 0.0222 g of the titled product.

Physical Characteristics of the titled product are as follows:

FAB mass spectrum. Found: $[m+H]^+$ at m/z 796. Measured = 796.4794.

EXAMPLE 5 $N_\alpha$-[(2S,4S,5S)-5-[N-[$N_\alpha$-(1-Naphthalenyloxy acetyl)-L-histidyl]amino]-6-cyclohexyl-4-(O-phosphoryl)-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide, trifluoroacetic acid salt or NOA-His-($OPO_3H_2$)CVA-Ile-Amp.

A mixture of flame-dried lithium chloride (0.020 g) and the product from Preparation 116 (0.100 g) in tetrahydrofuran (5 ml) is stirred, under nitrogen at ambient temperature for 18 hr; the solids have dissolved to give a gel. This mixture is then treated with 1H-tetrazol (0.053 g) and di-tert-butyl N,N-diethylphosphoramidite (0.11 ml) and stirred at ambient temperature for 24 hr. Additional 1H-tetrazol (0.053 g) and di-tert-butyl N,N-diethylphosphoramidite (0.11 ml) are added and stirring is continued for 24 hr. The mixture is then cooled in an ice bath, treated during 2.5 min with a solution of 85% m-chloroperoxybenzoic acid (0.154 g) in methylene chloride (3 ml), stirred for 20 min and treated with 10% aqueous sodium bisulfite (6.15 ml). It is then extracted with methylene chloride, the extract is concentrated in vacuo and the residue chromatographed on silica gel with 5% methanol - 0.5% ammonium hydroxide-methylene chloride to yield 0.0382 g of $N_\alpha$-[(2S,4S,5S)-5-[N-[$N_\alpha$-(1-naphthalenyloxyacetyl)-L-histidyl]amino]-6-cyclohexyl-4-(O-di-tert-butyl phosphoryl)-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide. A stirred solution of this product (0.025 g) in tetrahydrofuran (0.2 ml), under nitrogen, is treated with concentrated hydrochloric acid (0.1 ml), kept at ambient temperature for 1.3 hr. and concentrated under a stream of nitrogen to one third of its original volume. The residue is treated with water (3 ml) and freeze dried to give a waxy solid. A portion of this material is chromatographed on a preparative HPLC column (see general Procedure E). Elution is isocratic at 83% solvent A:17% solvent B for 15 min. followed by a linear gradient to 32% solvent A:68% solvent B over 90 min; the flow rate is 3 ml/min. The pure titled product is thus obtained.

Physical characteristics of the titled product are as follows:

FAB mass spectrum:found $[M+H^+$ at m/z 876, measured 876.4446.

EXAMPLE 6 1-Naphthoxyacetyl-L-histidyl-5S-amino-6-cyclohexyl-3R,4R-O,O-phosphoryl-2R-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide (Formula A-3) Refer to Chart A.

8 mg of lithium chloride is flame-dried under reduced pressure and allowed to cool to room temperature under argon. To this material is added 40 mg of 1-naphthoxyacetyl-L-histidyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide A-1 prepared as described in PCT International Publication No. WO 87/05302, published 11 September 1987, and 21 mg of 1H-tetrazole, followed by 0.5 mL of anhydrous tetrahydrofuran. After stirring for 30 min, 42 $\mu$L of di-*tert*-butyl N,N-diethyl-phosphoramidite is added and the resulting mixture is allowed to stir overnight. The reaction mixture is cooled to 0° and 30 mg of 85% *m*-chloroperbenzoic acid in a small amount of dichloromethane is added. After 20 min, additional dichloromethane and methanol is added to give a clear solution, and then excess aqueous sodium bisulfite is added. The reaction mixture is extracted with dichloromethane with a small amount of methanol. The organic phase is dried (magnesium sulfate) and then concentrated. The residue is chromatographed on silica gel with 5%-10% methanol in dichloromethane to give 13.2 mg of 1-naphthoxyacetyl-L-histidyl-5S-amino-6-cyclohexyl-3R,4R-O,O-tert-butyloxyphosphoryl-2R-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide (A-2). $^1$H-NMR spectrum is consistent with the proposed structure. FAB-MS: [M+H]+ at m/z 930 for $C_{49}H_{68}N_7O_9P$.

To a stirred solution of 13 mg of 1-naphthoxyacetyl-L-histidyl-5S-amino-6-cyclohexyl-3R,4R-O,O-tert-butyloxyphosphoryl-2R-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide (A-2) in 0.4 mL of tetrahydrofuran is added 0.2 mL of concentrate hydrochloric acid. After 1 hr, the mixture is concentrated and the residue evaporated with two portions of ethanol to give 12 mg of the titled product.

Physical characteristics of the titled product are as follows:

FAB-MS: [M+H]+ at m/z 874 for $C_{45}H_{60}N_7O_9P$.

$^1$H-NMR spectrum is consistent with the proposed structure.

CV-1 Assay (% Inhibition): 86% at 10$\mu$M; 24% at 1$\mu$M.

PREPARATION 116a tert-Butyloxycarbonyl-L-seryl-2-pyridylmethylamide (Formula B-3) Refer to Chart B.

To a stirred solution of 410 mg of tert-butyloxycarbonyl-L-serine (B-1) and 0.23 mL of 2-pyridylmethylamine (B-2) in 8 mL of dimethylforamide is added 0.44 mL of diisopropylethylamine and 986 mg of benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate. After stirring overnight, the concentrated reaction mixture is chromatographed on silica gel with 4%-8% methanol in dichloromethane to give 700 mg of the

titled product.

Physical characteristics of the titled product are as follows:

$^1$H-NMR spectrum is consistent with the proposed structure.

PREPARATION 117 L-Seryl-2-pyridylmethylamide (Formula B-4) Refer to Chart B.

A solution of 700 mg of the titled product of Preparation 116a in 4 mL of dichloromethane and 4 mL of trifluoroacetic acid is allowed to stir for 1 hr. The reaction mixture is added slowly to 200 mL of 2:1=ether:hexane. The residue is evaporated with toluene to give 700 mg of the bis trifluoroacetate salt of the titled product.

Physical characteristics of the titled product are as follows:

$^1$H-NMR spectrum is consistent with the proposed structure.

PREPARATION 118 5S-tert-Butyloxycarbonylamino-4S-tert-butyldimethylsilyloxy-6-cyclohexyl-2S-isopropyl-hexanoyl-L-seryl-2-pyridylmethylamide (Formula B-5) Refer to Chart B.

To a stirred solution of 700 mg of the titled product of Preparation 117 and 1.4 mL of diisopropylethylamine in 8 mL of dimethylforamide is added 1.21 g of 5S-tert-butyloxycarbonylamino-4S-tert-butyldimethylsilyloxy-6-cyclohexyl-2S-isopropyl-hexanoic acid and 1.1 g of benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate. After stirring overnight, the concentrated mixture is chromatographed on silica gel with 4%-8% methanol in dichloromethane to give 1.3 g of the titled product.

Physical characteristics of the title product are as follows:

FAB-MS: [M+H]+ at m/z 663 for $C_{35}H_{62}N_4O_6Si$.

$^1$H-NMR spectrum is consistent with the proposed structure.

PREPARATION 119 5S-Amino-4S-tert-butyldimethylsilyloxy-6-cyclohexyl-2S-isopropyl-hexanoyl-L-seryl-2-pyridylmethylamide (Formula B-7) Refer to Chart B.

A solution of 215 mg of the titled product of Preparation 118 in 1 mL of dichloromethane and 1 mL of trifluoroacetic acid is allowed to stir for 1 hr. The reaction mixture is partitioned between dichloromethane and aqueous sodium bicarbonate. The organic phase is dried (magnesium sulfate) and then concentrated to give 184 mg of the titled product.

Physical characteristics of the titled product are as follows:

$^1$H-NMR spectrum is consistent with the proposed structure.

PREPARATION 120 1-Naphthoxyacetyl-$N^{im}$-tert-butyloxycarbonyl-L-histidyl-5S-amino-4S-tert-butyldimethylsilyloxy-6-cyclohexyl-2S-isopropyl-hexanoyl-L-seryl-2-pyridylmethylamide (Formula B-8) Refer to Chart B.

To a stirred solution of 160 mg of 1-naphthoxyacetyl-$N^{im}$-tert-butyloxycarbonyl-L-histidine B-6 and 184 mg of the titled product of Preparation 119 in 1 mL of dimethylforamide

is added 80 μL of diisopropylethylamine and 180 mg of benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate. After stirring overnight, the concentrated reaction mixture is chromatographed on silica gel with 4%-8% methanol in dichloromethane to give 184 mg of the titled product.

Physical characteristics of the titled product are as follows:

FAB-MS: [M+H]+ at m/z 9843 for $C_{53}H_{77}N_7O_9Si$.

$^1$H-NMR spectrum is consistent with the proposed structure.

PREPARATION 121 1-Naphthoxyacetyl-$N^{im}$-tert-butyloxycarbonyl-L-histidyl-5S-amino-4S-tert-butyldimethylsilyloxy-6-cyclohexyl-2S-isopropyl-hexanoyl-O-di-tert-butylphosphate-L-seryl-2-pyridylmethylamide (Formula B-9) Refer to Chart B.

To a stirred solution of 49 mg of the titled product of Preparation 120 and 21 mg of 1H-tetrazole in 0.5 mL of tetrahydrofuran is added 42 μL of di-tert-butyl N,N-diethylphosphoramidite. After stirring at room temperature overnight, the reaction mixture is cooled to 0°C and 50 mg of 85% m-chloroperbenzoic acid in a small amount of dichloromethane is added. After 30 min, excess aqueous sodium bisulfite is added and the resulting mixture extracted with dichloromethane. The organic phase is dried (magnesium sulfate) and then concentrated. The residue is chromatographed on silica gel with 4%-8% methanol in dichloromethane to give 45 mg of the titled product.

Physical characteristics of the titled product are as follows:

FAB-MS: [M+H]+ at m/z 1176 for $C_{61}H_{94}N_7O_{12}PSi$.

$^1$H-NMR spectrum is consistent with the proposed structure.

EXAMPLE 7 1-Naphthoxyacetyl-L-histidyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-O-phosphoryl-L-seryl-2-pyridylmethylamide (Formula B-10) Refer to Chart B.

To a stirred solution of 45 mg of the titled product of Preparation 121 in 0.5 mL of dichloromethane is added 0.5 mL of trifluoroacetic acid. After 2 hr, the reaction mixture is slowly added to 80 mL of 2:1 = hexane:ether. The resulting mixture is centrifuged and the supernatant removed. The residue is washed with 2:1 = hexane:ether and then dried to give 17.8 mg of the titled product.

Physical characteristics of the titled product are as follows:

FAB-MS: [M+H]+ at m/z 850 for $C_{42}H_{56}N_7O_{10}P$.

$^1$H-NMR spectrum is consistent with the proposed structure.

PREPARATION 122 3-[3(R)-[3-(tert-Butyloxycarbonyl)-2,2-dimethyl-4(S)-(2-methyl-cyclohexyl)-5(R)-oxazolidinyl]-3-hydroxy-2(R)-isobutyl-1-oxopropyl]-4(R)-methyl-5(S)-phenyl-2-oxazolidinone (Formula C-3) Refer to Chart

C.

To a flame-dried flask under an atmosphere of argon gas containing 623 mg of 4(R)-methyl-3-(1-oxo-4-methylpentyl)-5(S)-phenyl-2-oxazolidinone (C-2) as a solution in 1.0 mL of dry dichloromethane at 0° is slowly added 2.50 mL of dibutylboron triflate and 0.47 mL of diisopropylethylamine. After 30 minutes the solution is cooled to -78° and 736 mg of 3-(tert-butyloxycarbonyl)-2,2-dimethyl-5(R)-formyl-4(S)-(2-methylcyclohexyl)oxazolidine (C-1) is added as a solution in 1.0 mL of dichloromethane with 2 x 0.5 mL rinses. After 30 minutes the reaction is warmed to room temperature for 2 hours. The mixture is then cooled to 0° and treated with 2.5 mL of 1.0 M phosphate buffer (pH=7), 5.0 mL of methanol and 2.5 mL of 30% aqueous hydrogen peroxide. The reaction is stirred for an additional hour, warmed to room temperature and partioned between dilute phosphate buffer and dichloromethane. The aqueous layer is extracted with additional portions of dichloromethane and the resulting organic layers are combined, dried (magnesium sulfate), and concentrated under reduced pressure. The residue is flash chromatographed (15% to 30% ethyl acetate in hexanes) on silica gel to afford 0.81 g of the titled product as a white foam.

Physical characteristics of the titled product are as follows:

$^1$H-NMR FAB HRMS: (300 MHz) 0.9-2.0, 0.95, 1.49, 1.52, 1.65, 2.61, 3.71, 3.84, 4.12, 4.83, 5.65, 7.4. $C_{34}H_{52}N_2O_7$ (m+H)=601.3882.

PREPARATION 123 3-[3(R)-[3-(tert-Butyloxycarbonyl)-2,2-dimethyl-4(S)-(2-methyl-cyclohexyl)-5(R)-oxazolidinyl]-3-hydroxy-2(R)-isobutyl-propanoic acid (Formula C-4) Refer to Chart C.

To a stirring solution of the 0.80 g of the titled product of Preparation 122 in 13 mL of methanol at 0° is added 0.85 mL of 30% aqueous hydrogen peroxide and 120 mg of lithium hydroxide hydrate in 7.0 ml water. The resulting cloudy mixture with precipitant is warmed to room temperature and stirred for 4 hours. The reaction is then diluted with diethyl ether and partioned against saturated aqueous sodium bicarbonate. The aqueous layer is extracted with an additional portion of diethyl ether and then acidified with 6 N hydrochloric acid employing methyl orange as an indicator. The acidic aqueous layer is re-extracted with diethyl ether (6x). The organic extraction layers are combined, dried (magnesium sulfate), and concentrated under reduced pressure. The residue is flash chromatographed on silica gel to afford 382 mg of the titled compound as a white solid.

Physical characteristics of the titled product are as follows:

$^1$H-NMR and FAB HRMS: (300 MHz) 0.9-1.9, 0.95, 1.47, 1.49, 1.62, 2.63, 3.72, 3.84, 3.95:$C_{24}H_{43}NO_6$ (m+H)=442.3196.

PREPARATION 124 3-[3(R)-[3-(tert-Butyloxycarbonyl)-2,2-dimethyl-4(S)-(2-methyl-cyclohexyl)-5(R)-oxazolidinyl]-3-hydroxy-2(R)-isobutyl-propanoyl-L-

isoleucyl-2-pyridylmethylamide (Formula C-6) Refer to Chart C.

To a stirring solution of 382 mg of the titled product of Preparation 123 and 290 mg of L-isoleucyl-2-pyridylmethylamine (C-5) in 8.0 mL of dichloromethane is added 0.30 mL of diisopropylethylamine and 0.20 mL of diethyl cyanophosphonate. After 4 days the reaction mixture is concentrated under reduced pressure. The residue is flash chromatographed (60% to 100% ethyl acetate in hexanes) on silica gel to afford 361 mg of the titled product as a white solid.

Physical characteristics of the titled product are as follows:

$^1$H-NMR and FAB HRMS: $C_{36}H_{60}N_4O_6$ (m+H)=645.4573.

PREPARATION 125 5S-Amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isobutyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide (Formula C-7) Refer to Chart C.

To a flask containing 5.0 mL of methanol at 0° is slowly added 0.36 mL of acetyl chloride. After 15 minutes the solution is warmed to room temperature and stirred for an additional 15 minutes. The methanolic hydrogen chloride is then added to a flask containing 361 mg of the titled product of Preparation 124. The solid dissolves and is left to stir at room temperature. After 7 hours the reaction mixture is diluted with dichloromethane and slowly treated with excess solid sodium bicarbonate. The cloudy suspension is stirred 2.5 hours, filtered through Celite with dichloromethane washings and finally concentrated under reduced pressure. The residue is gravity chromatographed (2% to 6% methanol in dichloromethane) on silica gel to afford 167 mg of the titled product as a white solid.

Physical characteristics are as follows:

$^1$H-NMR and FAB MS: $C_{28}H_{48}N_4O_4$ (m+H)=505.

PREPARATION 126 Cyclohexanecarbonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isobutyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide (Formula C-8) Refer to Chart C.

To a stirring solution of 40 mg of the titled product of Preparation 20 and 16 mg of cyclohexylcarboxylic acid in 0.8 mL of dichloromethane is added 26 μL of diisopropylethylamine and 18 μL of diethylphosphoryl cyanide. After 4 days the reaction mixture is concentrated under reduced pressure. The residue is gravity chromatographed (2% to 6% methanol in dichloromethane) on silica gel to afford 25 mg of the titled product as a white solid.

Physical chracteristics of the titled product are as follows:

$^1$H-NMR and FAB HRMS: $C_{35}H_{58}N_4O_5$ (m+H)=615.4480.

By following a similar procedure, the compound cyclohexanecarbonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or cyclohexane-carbonyl-CVD-Ile-Amp may be prepared.

PREPARATION 127 tert-Butyl-O-(4-quinolinyl)-glycolic carboxylate (Formula D-2) Refer to Chart D.

To a flame-dried flask under an atmosphere of argon gas is added 206 mg of potassium hydride (35% wt/oil). The hydride is washed with diethyl ether (2x), dried under high vacuum, and suspended in 5.0 mL of dry tetrahydrofuran. The flask is then slowly treated with 145 mg of 4-hydroxyquinoline (D-1) in portions. A white precipitant quickly forms. After 15 minutes the mixture is treated with 0.23 mL of tert-butylbromoacetate. The resulting pale orange solution is left to stir at room temperature for 3 days. The suspension is then slowly treated with methanol and filtered through Celite with dichloromethane washings. The filtrate is concentrated under reduced pressure. The residue is flash chromatographed (2% to 6% methanol in dichloromethane) on silica gel to afford 120 mg of the titled product as pale yellow crystals.

Physical characteristics of the titled product are as follows:

$^1$H-NMR (300 MHz) 1.43, 4.68, 6.27, 7.20, 7.38, 7.47, 7.64, 8.44

MS (EI) m/e 259 (M+).

PREPARATION 128 O-(4-Quinolinyl)-glycolic acid (Formula D-3) Refer to Chart D.

To a flask containing 120 mg of the titled product of Preparation 127 is added 5.0 mL of 1:1 trifluoroacetic acid and dichloromethane. The solid quickly dissolves and is left to stir at room temperature. After 2 hours the solution is slowly added to 100 mL of 1:2 diethyl ether:hexanes in a dropwise fashion. A white precipitant forms which is then centrifuged, washed with diethyl ether:hexanes, and finally dried under high vacuum to afford 117 mg of the titled product as the off-white trifluoroacetate salt.

Physical characteristics of the titled product are as follows:

FAB-MS: $C_{11}H_9NO_3$ (m+H)=204.

PREPARATION 129 N-(4-Quinolinyl)oxyacetyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide (Formula D-5) Refer to Chart D.

To a suspension of 26 mg of the titled product of Preparation 128 trifluoroacetate salt and 64 mg of 5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide (D-4) in 1.0 mL of dichloromethane is added 65 $\mu$L of diisopropylethylamine and 25 $\mu$L of diethylphosphoryl cyanide and 1.25 mL of dimethylformamide is added. After 3 days the reaction mixture is concentrated under reduced pressure. The resulting residue is flash chromatographed (4% to 15% methanol in dichloromethane) on silica gel to afford 15 mg of the titled compound as a white solid.

Physical characteristics of the titled product are as follows:

$^1$H-NMR and FAB-HRMS: $C_{38}H_{53}N_5O_5$ (m+H)=660.4113.

HIV-1 Protease ($K_I$, nM): >250.

PREPARATION 130 3-Aminoquinuclidine (Formula E-1) Refer to Chart E.

To as stirred suspension of 243 mg of sodium hydroxide in ca 1 ml of methanol is added 605 mg of 3-aminoquinuclidine dihydrochloride. The mixture is stirred for one hour, during which time the granular solid hydroxide is replaced by a finer white precipitate. Following removal of excess methanol, the residue is triturated with ether, the mixture filtered through Celite, and the solvent removed under reduced pressure. The residue is purified by sublimation at ca 0.1 Torr and 100° to yield 289 mg of the titled product as a feathery white solid.

PREPARATION 131 3R-Quinuclidineaminocarbonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide (Formula E-3) and 3S-Quinuclidineaminocarbonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide (Formula E-4) Refer to Chart E.

To a stirred solution of 51 mg of p-nitrophenyl choroformate in 0.5 ml of dichloromethane is added a solution of 32 mg of the titled product of Preparation 130 in 0.5 ml of dichloromethane. The resulting yellow solution is stirred for one hour, then 44 μL of diisopropylethylamine is added. After another 20 minutes, this mixture, which contains some precipiate, is added to 41.4 mg of 5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide (E-2). The resulting solution is stirred overnight, and then washed with aqueous alkali, with additional dichloromethane extracts of the aqueous layer. Combined organics are dried (magnesium sulfate) and then concentrated under reduced pressure. Chromatography of the material on silica with 5-12% methanol (saturated with ammonia) in dichloromethane provides 5.7 mg of isomer A, assigned formula E-3, 7.9 mg of isomer B, assigned formula E-4, and 7.4 mg of mixed fractions (total 20.9 mg).

Isomer A: FAB-MS (found): 643;

CV-1 Assay (% Inhibition): 12% at 1 μM.

Isomer B: FAB-MS (found): 643.4535;

CV-1 Assay (% Inhibition): 20% at 1 μM.

PREPARATION 132 Tert-butyloxycarbonyl-Ile-2-aminomethylpyridine.

Tert-butyloxycarbonyl-Ile and 1.03 mL freshly opened or distilled 2-aminomethylpyridine are dissolved in 7 mL dry N,N-dimethylformamide (stored over 4 Å molecular sieves) and 1.04 mL N,N-diisopropylethylamine, followed by addition of 4.87 g benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate. The reaction is stoppered and stirred 3 hr-overnight and monitored by Thin layer chromatography. Prior to workup, N,N-dimethylformamide is removed in vacuo. The resulting residue is dissolved in ethyl acetate, the

organic phase washed with aqueous sodium carbonate, dilute acetic acid, water, dried over sodium sulfate and then concentrated to yield 3.28 g oily residue which solidified upon standing at room temperature overnight.

Physical characteristics of the titled product are as follows:

Thin layer chromatography (silica gel Gf):Rf = 0.4 in 5% methanol/94% chloroform/1% acetic acid;

Rf = 0.4 in 10% N,N-dimethylformamide/90% toluene

(Visualized with ninhydrin or uv)

1H NMR ($CDCl_3$):8.53, 7.66, 7.26, 7.19, 5.13, 4.57, 4.06, 1.93, 1.43, 1.16, 0.90.

PREPARATION 133 Tert-butyloxycarbonyl-ChaΨ[CH(Otert-butyldimethylsilyl) $CH_2$]Val-Ile-2-aminomethylpyridine.

The titled product of Preparation 132 is dissolved in 5-10 ml of newly prepared hydrochloric acid-saturated methanol (prepared by bubbling anhydrous hydrochloric acid into methanol for about twenty minutes). After 20-30 minutes, this mixture is concentrated in vacuo and the residue examined by high performance liquid chromatography to determine completion of the deprotection reaction.

Physical characteristics of the product, H-Ile-2-aminomethylpyridine, are as follows:

Thin layer chromatography (silica gel GF):Rf=0.10 in 10% N,N-dimethylformamide/toluene; origin spot in 2:1 ethyl acetate:hexane and in 5% methanol/94% chloroform/1% $NH_4OH$.

$^1H$ NMR ($CDCl_3$):8.55, 8.19, 6.66, 7.28, 7.19, 4.58, 3.38, 2.00-2.06, 1.38-1.46, 1.08-1.18, 0.98, 0.89.

The above H-Ile-2-aminomethylpyridine is then dissolved in 25 ml dry N,N-dimethylformamide and 9.8 ml N,N-diisopropylethylamine (7.29 g). Tert-butyloxycarbonyl-ChaΨ[CH(O-tert-butyldimethylsilyl)$CH_2$]Val-OH (5.01 g) and benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate reagent (4.56 g) are added and the reaction stoppered and stirred at room temperature overnight. The reaction is concentrated in vacuo to remove the N,N-dimethylformamide and the resulting residue dissolved in ethyl acetate and washed with sat. sodium carbonate. The aqueous phase is re-extracted with ethyl acetate and the combined organic phases washed with saturated sodium chloride, dried over sodium sulfate, and concentrated in vacuo to yield 7.7 g brown gum. This material is purified by loading on a 46 x 4.6 cm silica gel flash column in ethyl acetate and eluting with 0.5 L each of 20%, 30%, 40%, 50%, and 60% ethyl acetate in hexane and 1.0 L each 66% and 70% ethyl acetate in hexane. The desired product (5.20 g) eluted at 70% ethyl acetate.

Physical characteristics of the titled product are as follows:

Thin layer chromatography (silica gel GF):Rf=0.22 in 70% ethyl acetate/hexane.

$^1$H NMR ($CDCl_3$):8.52, 7.63, 7.23, 6.09, 4.55, 4.39, 3.56-3.71, 2.13, 1.66-1.87, 1.43, 1.17-1.29, 0.90, 0.11.

MS (FAB):689 [M + H]$^+$, 589, 462, 236, 222, 109, 86, 57.

IR (mineral oil mull):2956, 2920, 2869, 2854, 1715, 1496, 1463 cm$^{-1}$.

PREPARATION 134 Hex-ChaΨ[CH(OH)$CH_2$]Val-Ile-2-aminomethylpyridine trifluoroacetic acid.

The amine resulting from the titled product of Preparation 133 is dissolved in 1 mL dry N,N-dimethylformamide and 523 μL (388 mg) of N,N-diisopropylethylamine. Hexanoic acid (69 μL) and benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (243 mg) are added and the reaction stood overnight at room temperature (after 1 hr, the reaction mixture had solidified). N,N-dimethylformamide is removed in vacuo. Extractive workup is identical to that performed previously in Preparation 132 and yielded 647 mg crude extract. One third of this amount is dissolved in 1 mL methanol and loaded on a 2 x 30 cm reverse phase C18 column and eluted with 10-40% CH3CN/0.1% trifluoroacetic acid in water to yield 26.4 mg product.

Physical characteristics of the titled product are as follows:

MS (FAB): 573 (M + H), 465, 352, 254, 236, 222, 109, 86.

HIV-1 Protease ($K_I$,nM): 47.

CV-1 Assay (% Inhibition): 67% at 10μM.

PREPARATION 135 Tert-butyloxycarbonyl-Ile-8-aminoquinoline.

Tert-butyloxycarbonyl-Ile (528 mg) is coupled to 8-aminoquinoline (288 mg) in 2 mL of dry N,N-dimethylformamide and 2.1 mL of N,N-diisopropylethylamine with benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (972 mg) at room temperature. The extractive workup is as previously described in Preparation 132 and the resulting residue is loaded on a silica gel flash column and eluted with 5% methanol/94% chloroform/1% acetic acid. One fraction contained pure product (177 mg); the rest were contaminated with unreacted 8-aminoquinoline.

Physical characteristics of the titled product are as follows:

Thin layer chromatography (silica gel GF): Rf=0.71 in 5% methanol/94% chloroform/1% acetic acid.

1H NMR ($CDCl_3$):8.77, 8.13, 7.52, 7.43, 5.45, 4.04, 1.55-1.68, 1.48, 0.93-1.06.

IR (mineral oil mull): 2057, 2026, 2856, 1709, 1672, 1529, 1506, 1485, 1173.

MS (EI): 284, 244, 186, 171, 144, 130, 57.

PREPARATION 136 Tert-butyloxycarbonyl-ChaΨ[CH(OH)$CH_2$]Val-Ile-8-aminoquinoline.

The titled product of Preparation 135 (168 mg) is deprotected with hydrochloric acid/methanol for 30-35 min, then concentrated in vacuo and monitored by hplc. The residue

is taken up in 1 mL dry N,N-dimethylformamide and 523 $\mu$L N,N-diisopropylethylamine (388 mg) and coupled to Tert-butyloxycarbonyl-Cha$\Psi$[CH(Otert-butyldimethylsilyl)$CH_2$]Val-OH (245 mg) with benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (243 mg) at room temperature overnight (high performance liquid chromatography indicated reaction is complete in 3 hr). Following an extractive workup as described above, 82 mg crude product is obtained; no purification is done.

Physical characteristics of the titled product are as follows:

Thin layer chromatography (silica gel Gf): Rf=0.62 in 50% ethyl acetate/50% hexane.

$^1$H NMR ($CDCl_3$):8.6-8.8, 8.1, 7.6-7.8, 7.3-7.6, 6.3, 4.5-4.8, 3.6-3.8, 3.2, 1.6-1.9, 1.44, 1.1-1.4, 0.91-1.00, 0.07-0.21.

MS (FAB):725 $[M + H]^+$, 625, 611, 481, 453, 412, 368, 171, 145, 86, 57.

PREPARATION 137 Acetyl-Cha$\Psi$[CH(OH)$CH_2$]Val-Ile-8-aminoquinoline.

Tert-butyloxycarbonyl-Cha$\Psi$[CH(Otert-butyldimethylsilyl)$CH_2$]Val-Ile-8-aminoquinoline (250 mg) the titled product of Preparation 136 is deprotected with hydrochloric acid/methanol and the resulting residue dissolved in 1 mL dry N,N-dimethylformamide and 600 $\mu$L N,N-diisopropylethylamine (445 mg). N-Acetyl-imidazole (228 mg) is added and the reaction stoppered and stirred at room temperature for 4 hr. N,N-dimethylformamide is removed in vacuo and the residue dissolved in ethyl acetate and washed with water. The aqueous phase is extracted twice with ethyl acetate, the combined organics washed with water, and dried over sodium sulfate to give 262 mg crude extract. Half of this extract is purified on a 2 x 30 cm reverse phase C18 column, eluted with 15-50% CH3CN/0.1% trifluoroacetic acid in water; 21.2 mg titled product is isolated along with 18.1 mg (16%) of diacetylated compound.

Physical characteristics of the titled product are as follows:

MS (FAB): 553 (M + H), 535, 409, 296, 258, 236, 145, 86.

HIV-1 Protease ($K_I$,nM): 61.

CV-1 Assay (% Inhibition):41%at 10$\mu$M.

PREPARATION 138 Tert-butyloxycarbonyl-Val-2-aminomethylpyridine.

Tert-butyloxycarbonyl-Val (478 mg) is coupled to 2-aminomethyl-pyridine in 1.6 mL dry N,N-dimethylformamide and 2 mL N,N-diisopropylethylamine with benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (942 mg) at room temperature. The extractive workup is as previously described in Preparation 132, and the resulting residue is loaded on a silica gel flash column and eluted with 3% methanol/94% chloroform/1% acetic acid to yield pure titled product (826 mg).

PREPARATION 139 Tert-butyloxycarbonyl-Cha$\Psi$[CH(O-tert-butyldimethylsilyl) $CH_2$]Val-Val-2-aminomethylpyridine.

The titled product of Preparation 138 (183 mg) is deprotected with 2 mL hydrochloric

acid/methanol for 20 min at room temperature, then concentrated in vacuo and monitored by high performance liquid chromatography. The residue is taken up in 0.5 mL dry N-N-dimethylformamide, 598 $\mu$L, N,N-diisopropylethylamine and coupled to Tert-butyloxycarbonyl-Cha$\Psi$[CH(Otert-butyldimethylsilyl)$CH_2$]Val-OH (240 mg) with benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (238 mg) at room temperature overnight. Following an extractive workup as described above, 431 mg crude titled product is obtained; no purification is done.

PREPARATION 140 Acetyl-Cha$\Psi$[CH(OH)$CH_2$]Val-Val-2-aminomethylpyridine.

The titled product of Preparation 139 (210 mg) is deprotected with hydrochloric acid/methanol for 200 min, concentrated in vacuo, and the resulting residue taken up in 1 mL dry N,N-dimethylformamide, 871 $\mu$L N,N-diisopropylethylamine. Acetyl-imidazole (330 mg) is added and the reaction stoppered and stirred at room temperature for 1.5 hr. N,N-dimethylformamide is then removed in vacuo and the residue dissolved in ethyl acetate and washed with water. The aqueous phase is extracted twice with ethyl acetate, the combined organic layers washed with water, and dried over sodium sulfate to give 272 mg crude product. Half of this material is purified on s 2 x 30 cm reverse-phase C18 column, eluted with 5-30% $CH_3CN$/0.1% trifluoroacetic acid in water; 22.4 mg titled product is isolated.

Physical characteristics of the titled product are as follows:

MS (FAB): 503 $[M + H]^+$ at m/z, 485, 395, 296, 254, 236, 208, 126, 109, 72.

HIV-1 Protease ($K_I$,nM):14.

CV-1 Assay (% Inhibition):54% at 10$\mu$M.

PREPARATIONS 141-165

Using the chemical procedures, starting materials and reactants described above, or methods analogous thereto, the following additional parent compounds for the compounds of the present invention, having the indicated physical characteristics are prepared:

(141) N$\alpha$-[(2S, 4S, 5S)-5-[N-(3-Indolymethylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide; or 3-Indolyl-$CH_2$-C(O)-CVA-Ile-Amp.

HR FAB MS $[m + H]^+$ at m/z 632.4162;

CV-1 Assay (% Inhibition): 33% at 10 $\mu$M.

(142) N$\alpha$-[(2S, 4S, 5S)-5-[N-(2-Indolycarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide; or 2-Indolyl-C(O)-CVA-Ile-Amp.

HR FAB MS $[m + H]^+$ at m/z 618.4021.

CV-1 Assay (% Inhibition): 85% at 10 $\mu$M.

(143) N$\alpha$-[(2S, 4S, 5S)-5-[N-[[2-(3-Indoly)ethyl]carbonyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide; or 3-Indolyl-$(CH_2)_2$-

C(O)-CVA-Ile-Amp.

HR FAB MS $[m + H]^+$ at m/z 646.4346.

CV-1 Assay (% Inhibition): 63% at 10 $\mu$M.

(144) Nα-[(2S, 4S, 5S)-5-[N-(3-Pyridinylmethylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide; or 3-Pyridinyl-$CH_2$C(O)-CVA-Ile-Amp.

HR FAB MS $[m + H]^+$ at m/z 594.4042.

CV-1 Assay (% Inhibition): 11% at 3 $\mu$M.

(145) Nα-[(2S, 4S, 5S)-5-[N-[(S)-Acetoxybenzylmethylcarbonyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide; or (S)-O-Acetyl-3-phenyllactyl-CVA-Ile-Amp.

HR FAB MS $[m + H]^+$ at m/z 665.4278.

CV-1 Assay (% Inhibition): 40% at 10 $\mu$M.

(146) Nα-[(2S, 4S, 5S)-5-[N-(4-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide; or 4-Pyridinyl-C(O)-CVA-Ile-Amp.

HR FAB MS $[m + H]^+$ at m/z 580.3858.

HIV-1 Protease ($K_I$, nM): 6.

CV-1 Assay (% Inhibition): 76% at 10 $\mu$M.

(147) Nα-[(2S, 4S, 5S)-5-[N-(4-Quinolinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide; or 4-Quinolinyl-C(O)-CVA-Ile-Amp.

HR FAB MS $[m + H]^+$ at m/z 630.4009.

CV-1 Assay (% Inhibition): 42% at 1 $\mu$M.

(148) Nα-[(2S, 4S, 5S)-5-[N-(3-Quinolinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide; or 3-Quinolinyl-C(O)-CVA-Ile-Amp.

HR FAB MS $[m + H]^+$ at m/z 630.4009.

CV-1 Assay (% Inhibition): 8% at 1 $\mu$M.

(149) Nα-[(2S, 4S, 5S)-5-[N-(3-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide; or 3-Pyridinyl-C(O)-CVA-Ile-Amp.

HR FAB MS $[m + H]^+$ at m/z 580.3886.

HIV-1 Protease ($K_I$, nM): 8.

CV-1 Assay (% Inhibition): 71% at 10 $\mu$M; 11% at 1 $\mu$M.

(150) Nα-[(2S, 4S, 5S)-5-[N-(2-Pyrrolylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-

1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide; or 2-Pyrrolyl-C(O)-CVA-Ile-Amp.
HR FAB MS $[m + H]^+$ at m/z 568.3888.
CV-1 Assay (% Inhibition): 79% at 10 $\mu$M.

(151) Nα-[(2S, 4S, 5S)-5-[N-(γ-L-Glutamyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide, trifluoroacetic acid salt; or γ-Glutamyl-CVA-Ile-Amp.
HR FAB MS $[m + H]^+$ at m/z 604.4081.
CV-1 Assay (% Inhibition): 14% at 10 $\mu$M.

(152) Nα-[(2S, 4S, 5S)-5-[N-(Succinoyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide, trifluoroacetic acid salt; or $HO_2C(CH_2)_2$-C(O)-CVA-Ile-Amp.
HR FAB MS $[m + H]^+$ at m/z 575.3803.
CV-1 Assay (% Inhibition): 11% at 10 $\mu$M.

(153) Nα-[(2S, 4S, 5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-(2, 4-diamino-6-pyrimidinylamino)ethyl]-L-isoleucinamide; or 2-Pyridinyl-C(O)-CVA-Ile-$NH(CH_2)_2$-NH-2,4-diamino-6-pyrimidinyl.
HR FAB MS $[m + H]^+$ at m/z 640.4306.
CV-1 Assay (% Inhibition): 15% at 10 $\mu$M.

(154) Nα-[(2S, 4S, 5S)-5-[N-(Glutaryl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide, trifluoroacetic acid salt; or $HO_2C(CH_2)_3$-C(O)-CVA-Ile-Amp.
HR FAB MS $[m + H]^+$ at m/z 589.3966.
CV-1 Assay (% Inhibition): 8% at 10 $\mu$M.

(155) Hydroxyacetyl-5S-amino-6-cyclohexyl-3R, 4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or (HO)Ac-CVD-Ile-Amp.
FAB-MS (found): 549.3628;
HIV-1 Protease ($K_i$, nM): 10.
CV-1 Assay (% Inhibition): 25% at 10 $\mu$M.

(156) L-Glycyl-5S-amino-6-cyclohexyl-3R, 4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide: or Gly-CVD-Ile-Amp.
FAB-MS (found): 548.3844;
HIV-1 Protease ($K_I$, nM): 182.

(157) Hydroxyacetyl-5S-amino-2R-benzyl-6-cyclohexyl-3R, 4R-dihydroxy-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or (HO) Ac-CPD-Ile-Amp.
FAB-MS (found): 597.3671

(158) Hydroxyacetyl-5S-amino-2R-benzyl-6-cyclohexyl-3R, 4R-dihydroxy-hexanoyl-L-

isoleucyl-2-pyridylmethylamide N-oxide; or (HO) Ac-CPD-Ile-Amp-NO.

FAB-MS (found): 613.3619;

HIV-1 Protease ($K_I$, nM): 250.

(159) L-Glycyl-5S-amino-2R-benzyl-6-cyclohexyl-3R, 4R-dihydroxy-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or Gly-CPD-Ile-Amp.

FAB-MS (found): 596.3835;

HIV-1 Protease ($K_I$, nM): >250.

(160) 1-Adamantanecarbonyl-5S-amino-6-cyclohexyl-3R, 4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or 1-Adamantanecarbonyl-CVD-Ile-Amp.

FAB-MS (found): 653.4666;

HIV-1 Protease ($K_I$, nM): >400;

CV-1 Assay (% Inhibition): 55% at 10 $\mu$M.

(161) Cyclohexanecarbonyl-5S-amino-6-cyclohexyl-3R, 4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or Cyclohexanecarbonyl-CVD-Ile-Amp.

FAB-MS (found): 601.4331;

HIV-1 Protease ($K_I$, nM): 22;

CV-1 Assay (% Inhibition): 80% at 10 $\mu$M.

(162) 5-Quinolinylhydroxyacetyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or 5-Quinolinylhydroxyacetyl-CVA-Ile-Amp.

FAB-MS (found): 660.4132;

CV-1 Assay (% Inhibition): 57% at 10 $\mu$M.

(163) Ac-CVA-Ile-O-benzyl; or Acetyl-5S-amino-6-cyclohexyl-2S-cyclohexylmethyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-O-benzylester.

FAB-MS $[m + H]^+$ (found): 51.;

HIV-1 Protease ($K_I$, nM): 121.5.

CV Assay (% Inhibition): 9% at 10$\mu$M.

(164) Ac-CVA-Ile-$NH_2$; or Acetyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucylamide.

FAB-MS $[m + H]^+$ (found): 426.

HIV-1 Protease ($K_I$, nM): 109;

CV-1 Assay (% Inhibition): 8% at 10 $\mu$M.

(165) Ac-CVA-Ile-aminomethyl-benzimidazole.

HIV-1 Protease ($K_I$, nM): 8;

CV-1 Assay (% Inhibition): 70% at 1 $\mu$M.

All of the parent compounds prepared in the Preparations above and below may be converted to the phosphate prodrug compounds of the present invention by following the

procedures in the Examples or methods analogous thereto.

EXAMPLE 8 N-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-(O-phosphoryl)-2-isopropyl-1-oxohexyl]-N-[(1S,2R)-2-hydroxy-1-indanyl]amine, trifluoroacetic acid salt; or 2Py CO CVP Ahi (Formula F-7) Refer to Chart F.

A. By the general procedure A for Boc group removal (1. $CF_3CO_2H$, 2. $NaHCO_3$), 0.3695 g of the Boc amine F-1 yields 0.329 g of the amine free base. The amine is then coupled (coupling procedure B) with picolinic acid (DEPC, $Et_3N$) and chromatographed over silica gel (1.2%MeOH:0.12%$NH_4OH$:$CH_2Cl_2$) to yield .371 g of coupled product F-2.

Physical characteristics are as follows:

The structure was supported by NMR and FAB mass spectra. Found: $[M+H]^+$ at *m/z* 664.

B. By the general procedure F for silyl ether cleavage, 0.3713 g of the silyl ether F-2 is allowed to react (1. $CF_3CO_2H$, 2. $NaHCO_3$) and then chromatographed over silica gel (2%MeOH:$CH_2Cl_2$) to yield first 0.2208 g of product F-3 as a mixture followed by 0.0451 g of pure crystalline product, m.p. 207-209°C. The mixture is rechromatographed over silica gel (1%MeOH:$CH_2Cl_2$ then 2%MeOH:$CH_2Cl_2$) to yield an additional 0.1528 g of crystalline F-3, N-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-[(1S,2R)-2-acetoxy-1-indanyl]amine; or 2Py CO CVA Aai.

Physical characteristics are as follows:

M.p. 211-212°C.

The structure was supported by a NMR and a high resolution FAB mass spectrum.

HR FAB MS $[M+H]^+$ m/z 550.3297.

HIV-1 Protease ($K_I$, nM): 220.

C. To a $N_2$-covered partial solution of 0.0451 g of F-3 in 3.3 mL of MeOH is added 6.6 mL of 5.4M $NH_3$/MeOH. Within 15 min everything dissolves and the solution is stirred at room temperature for 25 hrs and then concentrated *in vacuo*. The residue is chromatographed over silica gel (2.5%MeOH:0.25%$NH_4OH$:$CH_2Cl_2$) to yield 0.0329 g of crystalline F-4, N-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-[(1S,2R)-2-hydroxy-1-indanyl]amine; or 2Py CO CVA Ahi.

Physical characteristics are as follows:

M.p. 183-196°C.

The structure was supported by a high resolution FAB mass spectrum.

HR FAB MS $[M+H]^+$ m/z 508.3164.

HIV-1 Protease ($K_I$, nM): 12.

D. To a $N_2$-covered solution of 0.080 g of F-3 in 7.0 mL of THF is added 0.12 g of 1H-tetrazole followed by 0.1975 g of diallyl-N,N-diethyl phosphoramidite (rinsed with a

little THF). After stirring the mixture at room temperature for 21.5hrs, there is added an additional 0.1906 g of the phosphoramidite. After stirring for an additional 5 hrs the reaction mixture is cooled in an ice bath and there is added over 2.5 min a solution of 0.36 g of 85% *m*-chloroperoxybenzoic acid in 6.7 mL of $CH_2Cl_2$. After stirring in the cold for 10 min there is added quickly 14.5 mL of 10% aqueous sodium sulfite. The mixture is diluted with 50 mL of $CH_2Cl_2$ and the aqueous layer is separated and washed twice with $CH_2Cl_2$. The organic layers are combined, dried over $MgSO_4$ and concentrated *in vacuo*. The residue is chromatographed over silica gel (1%MeOH:0.1%$NH_4OH$:$CH_2Cl_2$ then 1.5%MeOH:0.15%$NH_4OH$:$CH_2Cl_2$) to yield first 0.0690 g of product F-5 followed by 0.0375 g of material that contains product F-5 as a part of a mixture (TLC and NMR).

Physical characteristics are as follows:

The structure was supported by NMR and FAB mass spectra. Found: $[M+H]^+$ at *m/z* 710.

E. To a $N_2$-covered solution of 0.0690 g of the diallylphosphonate ester F-5 in 1.6 mL of THF is added 6.4 mg of triphenylphosphine, 17.0 mg of tetrakis(triphenylphosphine) palladium (O) and then a solution of 0.018 mL of formic acid and 0.048 mL of *n*-butylamine in 1.6 mL of THF (added over 30 sec). After stirring at room temperature for 30 min there is added 24.3 mL of 0.01N KOH. The mixture is concentrated *in vacuo* to remove the THF. The aqueous residue is extracted twice with EtOAc:$Et_2O$ (emulsion). The aqueous layer that eventually separates is lyophilized and submitted to preparative HPLC according to procedure E to yield 0.0318 g of product F-6.

Physical characteristics are as follows:

The structure was supported by a FAB mass spectrum. Found: $[M+H]^+$ at *m/z* 630.

F. To a solution of 0.0318 g of the acetate F-6 in MeOH (2 mL) is added 4 mL of 5.4M $NH_3$/MeOH. There is also added 4.4 mL of 5.4M$NH_3$/MeOH at intervals of 3 days and 6 days. After a total of 7 days stirring the reaction mixture is concentrated *in vacuo*. The residue is submitted to preparative HPLC according to procedure E to yield 0.0234 g of the titled product F-7.

Physical characteristics are as follows:

The structure was supported by a high resolution FAB mass spectrum.

HR FAB MS $[M+H]^+$ m/z 588.2849.

HIV-1 Protease ($K_I$, nM): 350.

PREPARATION 166 N-[(2S,4S,5S)-5-[N-[(2-Pyridinyl)methoxycarbonyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-[(1S,2R)-2-hydroxy-1-indanyl]amine; or 2Poc CVA Ahi (Formula G-7) Refer to Chart G.

A. By the coupling procedure C, 0.300 g of G-1 is allowed to react with 1S-

amino-2R-hydroxyindane (DEPC, $Et_3N$) and then chromatographed over silica gel (1.25%MeOH:$CH_2Cl_2$) to yield 0.399 g of coupled product G-2.

Physical characteristics are as follows:

The structure was supported by NMR and FAB mass spectra. Found: $[M+H]^+$ at *m/z* 617.

B. To a $N_2$-covered ice bath cooled solution of 0.3991 g of the alcohol G-2 in 7.3 mL of pyridine is added 0.011 g of 4-dimethylaminopyridine followed by 0.58 mL of acetic anhydride (added over 45 sec). The solution is allowed to warm to room temperature and after stirring for 22 hrs is cooled again in an ice bath and treated over 1.25 min with 0.52 mL of MeOH. After stirring for 25 min in the cold, the reaction is pipetted into 40 mL of cold 1:1 $H_2O$:brine and extracted 3x with EtOAc. The combined extracts are washed 2x with 20 mL cold 0.5N HCl, 1x with $H_2O$, 1x with aqueous $NaHCO_3$ and 1x with brine. Each aqueous wash is backwashed with EtOAc. The combined organic fractions are dried over $MgSO_4$ and concentrated *in vacuo*. The residue is placed under house vacuum for 18 hr and then chromatographed over silica gel (15%EtOAc:hexane) to yield 0.377 g of product G-3.

Physical characteristics are as follows:

The structure was supported by NMR and FAB mass spectra. Found $[M+H]^+$ at *m/z* 659.

C. By the general procedure A for Boc group removal (1. $CF_3CO_2H$, 2. $NaHCO_3$), 0.4341 g of the Boc amine G-3 yields 0.386 g of the amine free base. To a $N_2$-covered solution of the amine in 4.8 mL of THF is added 0.17 mL of diisopropylethylamine. The mixture is cooled in an ice-MeOH bath and there is added over 3 min a solution of 0.14 g of 4-nitrophenylchloroformate in 9.6 mL of THF. After stirring in the cold for 21 hrs the mixture is concentrated *in vacuo*. The residue is chromatographed over silica gel (0.5%MeOH:$CH_2Cl_2$) to yield 0.2889 g of the carbamate G-4.

Physical characteristics are as follows:

The structure was supported by NMR and FAB mass spectra. Found $[M+H]^+$ at *m/z* 724.

D. To a $N_2$-covered solution of 0.2889 g of the urethane G-4 in 6.4 mL of dioxane is added 0.061 mL of triethylamine followed by 0.077 mL of 2-pyridylcarbinol. The mixture is heated in an oil bath at 95-100°C for 20 hrs and then concentrated *in vacuo*. The residue is chromatographed over silica gel (0.5%MeOH:$CH_2Cl_2$ followed by 2.5%MeOH:$CH_2Cl_2$) to yield first 0.10 g of a mixture (A) of starting urethane and *p*-nitrophenol (NMR) followed by 0.138 g of product G-5. In an effort to obtain additional product, a solution of mixture A in 2.2 mL of dioxane is treated with 0.021 mL of triethylamine and 0.027 mL of 2-pyridylcarbinol and heated at 100°C in an oil bath for 24hrs. After cooling the reaction

mixture is concentrated *in vacuo* and the residue is chromatographed over silica gel (0.5%MeOH:$CH_2Cl_2$, then 0.75%MeOH:$CH_2Cl_2$, then 2%MeOH:$CH_2Cl_2$) to yield 0.0382 g of additional product G-5.

Physical characteristics are as follows:

The structure was supported by NMR and FAB mass spectra. Found: $[M+H]^+$ at *m/z* 694.

E. By procedure F for silyl ether cleavage, 0.1762 g of the silyl ether G-5 is allowed to react (1. $CF_3CO_2H$, 2. $NaHCO_3$) and then chromatographed over silica gel (3%MeOH:0.3%$NH_4OH$: $CH_2Cl_2$) to yield 0.0931 g of product G-6.

Physical characteristics are as follows:

The structure was supported by a FAB mass spectrum. Found: $[M+H]^+$ at *m/z* 580.

F. To a solution of 0.030 g of the acetate G-6 in 2.0 mL of MeOH is added 4.0 mL of 5.4M $NH_3$ in MeOH. After stirring for 18 hrs at room temperature, an additional 4 mL of 5.4M $NH_3$ in MeOH is added. After stirring for an additional 23 hrs, the reaction mixture is concentrated *in vacuo*. The residue is chromatographed over silica gel (3%MeOH:0.3%$NH_4OH$:$CH_2Cl_2$) to yield 0.0197 g of product G-7.

Physical characteristics are as follows:

The structure was supported by a high resolution FAB mass spectrum.

HR FAB MS $[M+H]^+$ m/z 538.3293.

HIV-1 Protease ($K_I$, nM): 40.5.

PREPARATION 167 Nα-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-[4-[(3-amino-2-pyridinyl)amino]-2-butenyl]-L-isoleucinamide; or 2Py CO CVA Ile Apb (Formula H-9)

Refer to Chart H.

A. To a solution of 5.0 g of *trans* 1,4-dibromo-2-butene H-1 in 30 mL of toluene is added 10.39 g of potassium phthalimide followed by 0.62 g of 18-crown-6. After heating in an oil bath at 100°C for 8 hrs the mixture is allowed to cool and stir at room temperature for 3 days. There is then added 5 mL of $H_2O$ and after stirring at room temperature for 1 hr a suspended solid is collected on a filter, washed with $H_2O$ and dried under vacuum to yield 8.40 g of product H-2, m.p. 219-227°C. This crude product is used as is in the next step.

Physical characteristics are as follows:

The structure was supported by EI mass spec. Found $M^+$ at *m/z* 346, and IR. Anal. Found: C, 68..67; H, 4.05; N, 7.89.

B. 8.40 g of the crude product H-2 from the previous reaction is suspended under $N_2$ in 150 mL of absolute EtOH with mechanical stirring. There is then added 2.35 mL of hydrazine hydrate and the well stirred mixture is heated in an oil bath at 70°C for 4 hr. The

oil bath is then removed and after stirring at room temperature for 1 hr the stirrer is turned off and the mixture is allowed to stand for 18 hr. A suspended solid is collected on a filter and washed twice with absolute EtOH. The combined filtrates are concentrated *in vacuo* and treated with ~400 mL of warm (steam bath) $H_2O$. Some undissolved solid is removed by filtration and washed with a small amount of $H_2O$. The combined filtrates are cooled in an ice bath and acidified with 8 mL of 6N HCl. A heavy precipitate is collected on a filter and washed with a small amount of $H_2O$. The combined filtrates are lyophilized to yield 3.04 g of product H-3 as the HCl salt.

Physical characteristics are as follows:

M.p. >300°C.

The structure was supported by NMR and FAB mass spectra. Found: $[M+H]^+$ at *m/z* 87.

C. To a partial solution of 0.200 g of the amine salt H-3 in 9 mL of $H_2O$ is added 0.126 g of potassium bicarbonate. To the resulting solution is added over 2.5 min, a solution of 0.30 g of di-*t*-butyldicarbonate in 8 mL of dioxane. After stirring at room temperature for 25 hrs and then at 100°C in an oil bath for 6 hrs. The solution is allowed to cool and stir for 18 hr at room temperature. The solution is then concentrated *in vacuo* and the residue placed under vacuum. The residue is dissolved in $CH_2Cl_2$:MeOH (2:1) treated with 0.2 mL of $Et_3N$ adsorbed onto silica gel and chromatographed over a 50 mL silica gel column (elution with 9% MeOH:0.5% $NH_4OH$:$CH_2Cl_2$) to yield 0.1040 g of product H-4.

Physical characteristics are as follows:

M.p. 153.5-157°C (dec).

The structure was supported by NMR and FAB mass spectra. Found: $[M+H]^+$ at *m/z* 187.

D. To a $N_2$-covered suspension of 0.050 g of the mono Boc-diamine H-4 in 2 mL of THF is added 0.088 mL of triethylamine followed by 0.067 g of 2-chloro-3-nitropyridine. After heating in an oil bath at 75°C for 16.5 hr the mixture is allowed to cool and concentrated *in vacuo*. The residue is chromatographed over a 50 mL silica gel column to yield .0662 g of product H-5.

Physical characteristics are as follows:

The structure was supported by NMR and FAB mass spectra. Found: $[M+H]^+$ at *m/z* 309.

E. By the general procedure A for Boc group removal (1. $CF_3CO_2H$, 2. $NaHCO_3$), 0.058 g of the Boc amine H-5 yields 0.0361 g of the amine free base. The amine is then coupled (coupling procedure C) with Boc(OTBDMS)CVAlleOH (using DEPC, $Et_3N$) and chromatographed over silica gel (1.8% MeOH:0.18% $NH_4OH$:$CH_2Cl_2$) to yield 0.1137 g of

coupled product H-6.

Physical characteristics are as follows:

The structure was supported by NMR and FAB mass spectra. Found: $[M+H]^+$ at *m/z* 789.

F. By the general procedure A for Boc group removal (1. $CF_3CO_2H$, 2. $NaHCO_3$), 0.1137 g of the Boc amine H-6 yields 0.1261 g of crude amine free base. The amine is then coupled (coupling procedure B) with picolinic acid (using DEPC, $Et_3N$) and chromatographed over silica gel (1.8% MeOH: 0.18% $NH_4OH$:$CH_2Cl_2$) to yield 0.0802 g of coupled product H-7.

Physical characteristics are as follows:

The structure was supported by NMR and FAB mass spectra. Found: $[M+H]^+$ at *m/z* 794.

G. To a $N_2$-covered solution of 0.0614 g of the nitro peptide H-7 in 1 mL of absolute EtOH is added 0.087 g of stannous chloride dihydrate. After heating in an oil bath at 70°C for 35 min the reaction mixture is allowed to cool and is pipetted into 10 mL of ice. The mixture is neutralized with solid $NaHCO_3$ and extracted 4x with 20-30 mL portions of $CH_2Cl_2$. The combined extracts are dried over $MgSO_4$ and concentrated *in vacuo* to yield residue A. The aqueous fraction is diluted with 10 mL of $H_2O$ and lyophilized. The lyophilizate is washed 5x with portions of $CH_2Cl_2$ and the combined washes are concentrated *in vacuo* to yield residue B. Residues A and B are combined and chromatographed over silica gel (3% MeOH: 0.3% $NH_4OH$:$CH_2Cl_2$) to yield 0.0370 g of the amine H-8.

Physical characteristics are as follows:

The structure was supported by NMR and FAB mass spectra. Found: $[M+H]^+$ at *m/z* 764.

H. By procedure F for silyl ether cleavage, 0.0370 g of the silyl ether H-8 is allowed to react (1. $CF_3CO_2H$, 2. $NaHCO_3$) and then chromatographed over silica gel (4% MeOH:0.4% $NH_4OH$:$CH_2Cl_2$) to yield 0.0199 g of the titled product.

Physical characteristics are as follows:

The structure was supported by a high resolution FAB mass spectrum.

HR FAB MS $[M+H]^+$ m/z 650.4411.

HIV-1 Protease ($K_I$, nM): 67.

EXAMPLE 9 Nα-[(2S,4S,5S)-5-[N-[(3-Pyridinyl)methoxycarbonyl]amino]-6-cyclohexyl-4-(O-phosphoryl)-2-isopropyl-1-oxohexyl]-N-(2-benzimidazolylmethyl)-L-isoleucinamide, trifluoroacetic acid salt; or 3Poc CVP Ile Amb (Formula I-9)

Refer to Chart I.

A. To a $N_2$ covered suspension of 1.0 g of 2(aminomethyl)benzimidazole I-1 in

225 mL of $CH_2Cl_2$ is added 1.250 g of Boc isoleucine followed by 2.37 mL of triethylamine. Within 5 min everything went into solution and there is added 0.97 mL of diethyl cyanophosphonate. After stirring at room temperature for 20.5 hr the reaction mixture is washed with aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. The residue is chromatographed over silica gel (3% MeOH:0.3% $NH_4OH$:$CH_2Cl_2$) to yield 1.50 g of crystalline product I-2.

Physical characteristics are as follows:

M.p. 213.5-214.5°C.

The structure was supported by NMR and FAB mass spectra. Found $[M+H]^+$ at *m/z* 361.

B. To a $N_2$ covered ice bath cooled partial solution of 0.464 g of the Boc amine I-2 in 3.1 mL of $CH_2Cl_2$ is added dropwise over 4 min 3.1 mL of trifluoroacetic acid. The ice bath is removed and after stirring at room temperature for 1 hr 7 min, the reaction mixture is added dropwise over 1.75 min to a well stirred mixture of 3.5 g $NaHCO_3$, 25 mL $H_2O$ + 50 mL $CH_2Cl_2$. The aqueous layer is washed twice with $CH_2Cl_2$ and the combined organic fractions are dried over $MgSO_4$ and concentrated *in vacuo* to yield 0.1658 g of crude amine free base A. The aqueous fraction is lyophilized and the lyophilizate is washed several times with $CH_2Cl_2$ to yield 0.1411 g of additional amine free base. This latter material is combined with amine A and coupled (coupling procedure C) with Boc(OTBDMS)CVA (using DEPC, $Et_3N$) and chromatographed over silica gel (3% MeOH:0.3% $NH_4OH$:$CH_2Cl_2$) to yield 0.6402 g of coupled product I-3.

Physical characteristics are as follows:

The structure was supported by NMR and FAB mass spectra. Found: $[M+H]^+$ at *m/z* 728.

C. By the general procedure A for Boc group removal (1. $CF_3CO_2H$, 2. $NaHCO_3$), 0.200 g of the Boc amine I-3 yields 0.176 g of crude amine free base. To a solution of 0.114 g of the mixed carbonate salt I-4 prepared as described in Preparation 168, in 1.3 mL of $CH_3CN$ is added 0.12 mL of diisopropyl-ethylamine. After stirring at room temperature for 10 min there is added a solution of the amine free base in 1.3 mL of $CHCl_3$ and after heating in an oil bath at 80°C for 16 hr the reaction is allowed to cool and concentrated *in vacuo*. The residue is chromatographed over silica gel (1.5% MeOH:0.15% $NH_4OH$:$CH_2Cl_2$ followed by 0.3% MeOH; 0.3% $NH_4OH$:$CH_2Cl_2$) to yield 0.128 g of the carbamate I-5.

Physical characteristics are as follows:

The structure was supported by NMR and FAB mass spectra. Found: $[M+H]^+$ at *m/z* 763.

D. By procedure F for silyl ether cleavage, 0.1278 g of the silyl ether I-5 is allowed to react (1. $CF_3CO_2H$, 2. $NaHCO_3$) and then chromatographed over silica gel (4%MeOH:0.4%$NH_4OH$:$CH_2Cl_2$ followed by 5%MeOH:0.5%$NH_4OH$:$CH_2Cl_2$) to yield 0.0924 g of the product I-6, Nα-[(2S,4S,5S)-5-[N-[(3-Pyridinyl)methoxycarbonyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-benzimidazolylmethyl)-L-isoleucinamide; or 3Poc CVA Ile Amb.

Physical characteristics are as follows:

The structure was supported a FAB mass spectrum. Found: $[M+H]^+$ at *m/z* 649.

HIV-1 Protease ($K_I$, nM): 10.

E. To a solution of 0.0924 g of the product I-6 in 5.0 mL of THF is added 0.12 g of 1H-tetrazole followed by a solution of 0.188 g of diallyl-N,N-diethylphosphoramidite I-7, prepared as described in Preparation 169, in 2.0 mL of THF. After stirring at room temperature for 2 days an additional 0.100 g of the phosphoramidite is added and after 5.5 hrs 0.187 g more phosphoramidite is added. Then after an additional 19 hr of stirring, the reaction mixture is cooled in an ice bath and there is added dropwise over 2.75 min a solution of 0.45 g of 85% *m*-chloroperoxybenzoic acid in 8.3 mL of $CH_2Cl_2$. After stirring in the cold for 10 min there is added quickly 18 mL of 10% aqueous sodium sulfite. The mixture is diluted with 50 mL of $CH_2Cl_2$. The aqueous fraction is extracted twice with $CH_2Cl_2$ and the combined organic fractions are dried over $MgSO_4$ and concentrated *in vacuo*. The residue is chromatographed over silica gel (4%MeOH:0.4%$NH_4OH$:$CH_2Cl_2$) to yield 0.0505 g of product I-8.

Physical characteristics are as follows:

The structure was supported by NMR and FAB mass spectra. Found: $[M+H]^+$ at *m/z* 809.

F. To a $N_2$-covered solution of 0.0505 g the phosphonate diester I-8 in 1.0 mL of THF is added 4.1 mg of triphenylphosphine and 11 mg of tetrakis (triphenylphosphine) palladium (O). There is then added dropwise over 1 min a solution of 0.012 mL of formic acid and 0.031 mL of *n*-butylamine in 1.0 mL of THF. After stirring at room temperature for 1 hr there is added 15.6 mL of 0.01N KOH and the mixture is concentrated *in vacuo* to remove the THF. A gummy precipitate present in the aqueous residue solidifies sufficiently when cooled in an ice bath to be collected on a filter. This filtered amorphous material is dissolved in MeOH and concentrated *in vacuo*. The residue is washed once with 1 mL of EtOAc and the material remaining is submitted to preparative HPLC according to procedure E to yield 23.7 mg of the titled product I-9.

Physical characteristics are as follows:

The structure was supported by a high resolution FAB mass spectrum.

HR FAB MS $[M+H]^+$ m/z 729.3746.

HIV-1 Protease ($K_I$, nM): 350.

PREPARATION 168 3-Pyridinylmethyl *p*-nitrophenyl carbonate, *p*-nitrophenol salt.

A $N_2$-covered solution of 0.81 mL of 3-pyridylcarbinol in 10 mL of benzene Is heated in an oil bath at reflux under a Dean Stark trap for 2 hrs. After cooling the solution is concentrated *in vacuo*. To a $N_2$-covered solution of the residue in 15 mL of $CH_2Cl_2$ is added 2.79 g of bis(*p*-nitrophenyl)carbonate. After stirring for 17.75 hrs the mixture is concentrated *in vacuo*. The residue is treated with 30 mL of $Et_2O$ and an undissolved solid is removed by filtration. The filtrate yields two crops, 2.073 g (m.p. 91.5-95°C) and 0.1259 g (m.p. 90.5-96°C) of the titled product.

Physical characteristics are as follows:

The analytical sample melted at 97.5-98°C.

The structure was supported by NMR, infrared and FAB mass spectra. Found $[M+H]^+$ at *m/z* 275. Anal. Found: C, 54.97; H, 3.56; N, 10.06.

PREPARATION 169 Diallyl N,N-diethylphosphoramidite (Formula J-3) Refer to Chart J.

A. To a $N_2$-covered solution of 7.47 mL of phosphorous trichloride J-1 in 50 mL of $Et_2O$, cooled to -30 to -50°C with intermittent use of a dry ice:$Me_2CO$ bath, is added over 35 min, 17.7 mL of neat diethylamine (caution-vigorous reaction). The reaction is then allowed to warm to room temperature and after 2 hr 10 min stirring, there is added an additional 50 mL of $Et_2O$. A precipitate is collected on a filter under $N_2$ and washed well with $Et_2O$. The combined filtrates are concentrated *in vacuo* and the residue is distilled at 8.5 mm to yield 11.18 g of product J-2.

Physical characteristics are as follows:

B.p. 69°C.

The structure was supported by a NMR spectrum.

B. The dichloride J-2 is dissolved in 50 mL of $Et_2O$ and cooled to -30 to -40°C with intermittent use of a dry ice:$Me_2CO$ bath. There is then added a solution of 8.75 mL of allyl alcohol and 19.7 mL of triethylamine in 50 mL of $Et_2O$ dropwise over 22 min. The reaction is then allowed to warm to room temperature and after stirring for 3 hrs there is added 25 mL of 5% aqueous $NaHCO_3$. The $Et_2O$ layer is separated and washed 2x with 20 mL portions of 5% aqueous $NaHCO_3$ and 1x with brine. The organic layer is concentrated *in vacuo* and the residue is distilled at 0.45 mm to yield 11.73 g of diallyl-N,N-diethylphosphoramidite.

Physical characteristics are as follows:

B.p. 53-56°C.

The structure was supported by $H^1$ and 31P NMR spectra.

EXAMPLE 10 1-naphthoxyacetyl-O-phosphoryl-L-threonyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine, dipotassium salt; or Noa-O-$PO_3K_2$-Thr-CVA-Ile-Amp (Formula K-6) Refer to Chart K.

A. Noa-Thr-CVA(OTBS)-Ile-Amp (Formula K-3)

To a stirring solution of 200 mg of Noa-Thr-OH (K-1) and 415 mg of H-CVA(OTBS)-Ile-Amp (K-2) in 3 mL of dichloromethane is added 310 mg of benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate followed by 130 $\mu$L of diisopropylethylamine. After 3 days, the reaction mixture is concentrated under reduced pressure to afford a viscious oil. The oil is flash column chromatographed on silica gel using 2% to 6% methanol in dichloromethane to afford the crude product also as an oil. The oil is dissolved in a large volume of diethyl ether, washed with water (3x), brine, dried ($MgSO_4$), and finally concentrated under reduced pressure to afford 370 mg of Noa-Thr-CVA(OTBS)-Ile-Amp (K-3).

B. Noa-Thr(OP(O)($OCH_2CH=CH_2)_2$)-CVA(OTBS)-Ile-Amp (Formula K-4)

To a flame-dried flask under an argon atomsphere is added 262 mg of Noa-Thr-CVA(OTBS)-Ile-Amp (K-3) and 105 mg of tetrazole. The solids are charged with 1.5 mL of dry tetrahydrofuran. The resulting solution is treated with 350 $\mu$L of diallyl N,N-diethylphosphoramidite. After 0.5 hour, the reaction is treated with an additional 100 $\mu$L of phosphoramidite reagent. After 0.75 hour total, the reaction mixture is cooled to -35 °C and treated with 470 mg of ~85% *m*-chloroperoxybenzoic acid as a solution in 4.5 mL of dichloromethane. After 15 minutes, the reaction is warmed to room temperature and diluted with 70 mL of diethyl ether. The mixture is washed with 10% aqueous sodium metabisulfate (2 x15 mL), followed by 5% aqueous sodium bicarbonate (2 x 15 mL), 5% aqueous citric acid (2 x 15 mL), and finally brine. The organic phase is dried ($MgSO_4$) and then concentrated under reduced pressure. The residue is flash column chromatographed on silica gel using 1% to 6% methanol in dichloromethane to afford 273 mg of Noa-Thr(OP(O)($OCH_2CH=CH_2)_2$)-CVA(OTBS)-Ile-Amp (K-4).

C. Noa-Thr(OP(O)($OCH_2CH=CH_2)_2$)-CVA-Ile-Amp (Formula K-5)

To a stirring solution of 273 mg of Noa-Thr(OP(O)($OCH_2CH=CH_2)_2$)-CVA(OTBS)-Ile-Amp (K-4) in 0.5 mL of dichloromethane is added 0.5 mL of trifluoroacetic acid. After 50 minutes, the reaction is diluted with additional dichloromethane and slowly added to excess aqueous sodium bicarbonate. After 0.33 hours, the phases are separated and the aqueous layer is extracted with additional portions of dichloromethane (4x). The combined organic extractions are dried ($MgSO_4$) and concentrated under reduced pressure. The residue is flash chromatographed on silica gel using 2% to 6% methanol in dichloromethane to afford 211 mg of Noa-Thr(OP(O)($OCH_2CH=CH_2)_2$)-CVA-Ile-Amp (K-5) as a white solid.

D. Noa-Thr(OP(O)$(OK)_2$)-CVA(OTBS)-Ile-Amp (Formula K-6)

To a flame-dried flask under an argon atomsphere containing a stirring solution of 211 mg of Noa-Thr(OP(O)$(OCH_2CH=CH_2)_2$)-CVA-Ile-Amp (K-5), 27 mg of tetrakis (triphenylphosphine)palladium(0) and 30 mg of triphenylphosphine in 7.5 mL of dry tetrahydrofuran, is added 43 μL of formic acid and 116 μL of *n*-butylamine as a solution in 0.5 mL of dry tetrahydrofuran. The clear tan solution slowly grows cloudy. After 1 hour, the reaction is treated with additional amounts of reagents: 20 mg of palladium catalyst, 25 mg triphenylphosphine, and 35 μL of formic acid along with 90 μL of butylamine in 0.5 mL of tetrahydrofuran. After an additional hour, the reaction is diluted with diethyl ether and partioned against 50 mL of 0.01 N aqueous potassium hydroxide. The aqueous layer is extracted with ethyl acetate and diethyl ether. The combined organic layers are back-extracted with dilute aqueous potassium hydroxide. The combined aqueous layers are filtered and lyophilized. The lyophile is dissolved in dilute aqueous potassium carbonate, extracted with *n*-butanol (4x), and the butanol extractions are concentrated under reduced pressure. The residue is dissolved in water and lyophilized. The lyophile is divided into lots, dissolved in a small amount of water, and processed through Sep-Pak $C_{18}$ cartridges eluting with 0% to 50% acetonitrile in water. The product fractions are concentrated and lyophilized to afford 114 mg of Noa-Thr(OP(O)$(OK)_2$)-CVA-Ile-Amp (K-6).

Physical characteristics are as follows:

FAB-MS: (m+H) = 916.3449.

HIV-1 Protease ($K_I$, nM): 73.

EXAMPLE 11 3-(O-phosphoryl-4-OH-phenyl)-butyryl-L-histidyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Dat(O-$PO_3H_2$)-His-CVA-Ile-Amp.

des-$NH_2$-O-phospho-L-tyrosine is prepared by reaction of 3-(p-hydroxyphenyl)-butyric acid with 4 equivalents of $P_2O_5$ in $H_3PO_4$ at 80 degrees for 24 hours (Paul F. Alewood, R.B. Johns and Robert M. Valerio, Synthesis, 30, 1983). The desired product is purified by reverse phase C18 chromatography and characterized by NMR and FAB/MS. The phosphorylated tyrosine analog is coupled to the N-terminus of the peptide using benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphoniumhexa-fluorophosphate (BOP reagent) for carboxylate activation. The phosphorylated peptide is purified by reverse phase chormatography and characterized by FAB/MS.

Physical characteristics are as follows:

FAB-MS: (M+H) = 839.9006.

HIV-1 Protease ($K_I$, nM): 8.1.

PREPARATION 170 ((5-(3,6,9,12,15-pentaoxa-hexadec-1-yl)oxy)naphthalen-1yl)oxyacetyl-L-

valinyl-5*S*-amino-6-cyclohexyl-3*R*,4*R*-dihydroxy-2*R*isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine; or 5-PentaegNoa-Val-CVD-Ile-Amp (Formula L-6) Refer to Chart L.

A. A solution of 40 mg of Boc-Val-OH (L-1) (Peptides International) and 53 mg of H-CVD-Ile-2-Amp (L-2) all in 2 ml of dimethylformamide is treated with 90 $\mu$l of diisopropylethylamine (Aldrich) followed by 40 $\mu$l of diethyl cyanophosphonate (Aldrich). The resulting colorless solution is allowed to stir at room temperature under a nitrogen atmosphere for 25 h at which time TLC analysis confirms the reaction is complete. This mixture is diluted with methanol and then concentrated under reduced pressure (first under house vacuum to remove methanol and then with a vacuum pump to remove dimethylformamide) to give the crude product as a light brown solid. This material is chromatographed over 50 g of silica gel (63-200$\mu$), eluting with 4% (4M $NH_3$/MeOH)/$CHCl_3$ and collecting 7 ml fractions. Fractions 28-40 are combined and concentrated to give 78 mg of L-3.

Physical characteristics are as follows:

TLC (Phosphomolybdic acid) R*f* = 0.45 in 5% (4M $NH_3$/MeOH)/$CHCl_3$.

B. The Boc-Val-CVD-Ile-2-Amp (L-3) from the previous experiment is treated with 3 ml of methylene chloride and 3 ml of trifluoroacetic acid (Aldrich). The resulting solution is stirred at room temperature for 2 h at which time TLC analysis indicates the reaction is complete. The solution is concentrated under reduced pressure to give the crude product as an oil. This material is chromatographed over 50 g of silica gel (63-200$\mu$), eluting with 5% (4M $NH_3$/MeOH)/$CHCl_3$ and collecting 7 ml fractions. Fractions 36-55 are combined and concentrated to give 58 mg of L-4.

Physical characteristics are as follows:

TLC (Phosphomolybdic acid) R*f* = 0.19 in 5% (4M $NH_3$/MeOH)/$CHCl_3$.

C. A solution of 64 mg of 5-[$CH_3O[CH_2CH_2O]_5$]-1-Noa (L-5), prepared as described in Preparation 171, and 58 mg of H-Val-CVD-Ile-2-Amp (L-4) all in 2 ml of dimethylformamide is treated with 83 $\mu$l of diisopropylethylamine (Aldrich) followed by 37 $\mu$l of diethyl cyanophosphonate (Aldrich). The resulting solution is allowed to stir at room temperature under a nitrogen atmosphere for 19 h at which time TLC analysis indicates no remaining amine. The solution is diluted with methanol and then concentrated under reduced pressure (first under house vacuum to remove methanol and then with a vacuum pump to remove dimethylformamide) to give the crude product as a dark brown oil. This material is chromatographed over 50 g of silica gel (63-200$\mu$), eluting with 3% (4M $NH_3$/MeOH)/$CHCl_3$ and collecting 6.5 ml fractions. Fractions 63-89 are combined and concentrated to give 74 mg of the titled product:

Physical characteristics are as follows:

MS (FAB, high resolution positive ion) *m/z* 1024.6236 $[M+H]^+$, other ions at *m/z* 916, 803, 534, 506, 270, 222, 126, 109, 86, 72 and 59. HPLC retention time = 19.4 min. TLC (Phosphomolybdic acid) R*f* = 0.16 in 6% (4M $NH_3$/MeOH)/$CHCl_3$. HIV-1 Protease ($K_I$, nM): 8.9.

PREPARATION 171 5-[$CH_3O[CH_2CH_2O]_5$]-1-Noa.

A. A mixture of pentaethylene glycol (0.21 ml; Aldrich) in 1.6 ml of hexane (the glycol) does not dissolve in this solvent and gives a two phase mixture) is treated with 0.40 ml of dihydropyran (Aldrich) and then with 22 mg of aluminum sulfate impregnated silica gel (3 mmoL aluminum sulfate/g silica gel) catalyst. This mixture is stirred under a nitrogen atmosphere for 1.5 h and then filtered through a sintered glass filter funnel, washing the collected solids with ethyl acetate. The combined filtrates are concentrated under reduced pressure to give a colorless oil. This material is chromatographed over 50 g of silica gel (63-200$\mu$), eluting with 5% MeOH/$CHCl_3$ and collecting 8 ml fractions. Fractions 24-31 are combined and concentrated to give the bis-tetrahydropyranyl adduct.

Physical characteristics are as follows:

$^1H$ NMR ($CDCl_3$) $\delta$ 4.64, 3.90-3.82, 3.70-3.50, 1.93-1.46. TLC (Sulfuric acid) R*f* = 0.68 in 10% MeOH/$CHCl_3$.

Fractions 42-140 afford the pure desired compound (THPO$(CH_2CH_2O)_5$H).

Physical characteristics are as follows:

$^1H$ NMR ($CDCl_3$) $\delta$ 4.64, 3.90-3.82, 3.70-3.50, 2.78, 1.93-1.46. TLC (Sulfuric acid) R*f* = 0.30 (elongated spot) in 10% MeOH/$CHCl_3$. [The column was stripped with ethyl acetate and this wash afforded some additional desired product along with unreacted glycol].

B. A 1.1 g mixture of products (no chromatographic separation) from the synthesis of THPO$(CH_2CH_2O)$H [i.e. THPO$(CH_2CH_2O)$H, THPO$(CH_2CH_2O)$THP and pentaethylene glycol] all in 5 ml of tetrahydrofuran is treated with excess methyl iodide (0.32 ml, Aldrich) followed by the portionwise addition of sodium hydride (0.20 g, 60% dispersion in mineral oil). The resulting mixture (under a nitrogen atmosphere) is let stir at room temperature for 19 h and then quenched with saturated aqueous ammonium chloride. This mixture is extracted with ethyl acetate (5x) and the combined organic extracts are dried (magnesium chloride), filtered, and concentrated under reduced pressure to give the crude product mixture (THPO$(CH_2CH_2O)$THP, THPO$(CH_2CH_2O)_5CH_3$ and $CH_3O[CH_2CH_2O]_5CH_3$ as a yellow oil. This material is combined with another lot of similarly prepared material and is used in the next experiment without purification or characterization.

C. A 7.0 g sample of the product mixture from the previous experiment is dissolved in 8 ml of tetrahydrofuran. This solution is treated with 1 ml of water and 1 ml of 1

N hydrochloric acid. The resulting solution is allowed to stir at room temperature for 2 h and then an additional 1 ml of water is added. Stirring is continued for 18 h at which time TLC analysis indicates only partial hydrolysis. Two additional ml of 1 N hydrochloric acid is added along with 5 ml of methanol. This solution is then heated to 60-65°C for 4.5 h. The orange colored solution is allowed to cool to room temperature and then neutralized to pH 7 by the dropwise addition of saturated aqueous sodium bicarbonate. This mixture is concentrated under reduced pressure to give an orange colored oil. This material is flash chromatographed on a silica gel (40-63$\mu$) column (35 mm OD x 40 cm), eluting with 50% acetone/hexane and collecting 140 ml fractions. Fraction 6-12 are combined and concentrated to give 1.52 g of pure monomethyl ether $HO(CH_2CH_2O)_5CH_3$.

Physical characteristics are as follows:

$^1H$ NMR ($CDCl_3$) $\delta$ 3.75-3.53, 3.38, 2.81; MS (EI) *m/z* 253 $[M]^+$(weak), 133, 103, 89, 59, and 45. TLC (Sulfuric acid) R*f* = 0.23 (elongated spot) in 50% acetone/hexane [this material gives only a very faint spot under these TLC conditions].

D. A solution of 1.52 g of $HO(CH_2CH_2O)_5CH_3$ in 5 ml of pyridine is placed under a nitrogen atmosphere and cooled to 0°C. This solution is then treated in one portion with 1.40 g of *p*-toluenesulfonyl chloride and the resulting solution is stirred at 0°C for 2.5 h (after about 30 min a milky suspension had formed). This mixture is poured into a cold (ice bath) solution of 5 ml concentrated hydrochloric acid and 15 ml of water and then extracted with ethyl acetate (3x). The combined organic extracts are washed with water (4x) with the pH of the final wash being adjusted to 7 by the addition of saturated aqueous sodium bicarbonate. The organic phase is dried (magnesium sulfate), filtered and concentrated to give the crude product ($TSO(CH_2CH_2O)_5CH_3$) as an orange colored oil.

Physical characteristics are as follows:

$^1H$ NMR ($CDCl_3$) $\delta$ 7.80, 7.34, 4.20-4.14, 3.73-3.53, 3.38, 2.45. TLC (Phosphomolybdic acid) R*f* = 0.55 in 50% acetone/hexane. This material was used directly in the next experiment without purification.

E. A solution of 1.02 g of $CH_3O[CH_2CH_2O]_5Ts$ and 0.38 g of 1,5-dihydroxynaphthalene (Aldrich) all in 20 ml of dimethylformamide is treated portionwise *via* a spatula with 0.21 g of sodium hydride (60% dispersion in mineral oil) (Aldrich) over 10 min while purging the system with nitrogen. The resulting mixture is heated to 50°C and stirred for 1.5 h. Methyl bromoacetate (0.45 ml) is then added *via* syringe and stirring and heating is continued for an additional 1.5 h. The solution is let cool and the reaction is quenched by the addition of saturated aqueous ammonium chloride. This mixture is diluted with methanol and then concentrated under reduced pressure (first under house vacuum to remove methanol and then with a vacuum pump to remove dimethylformamide) to give a greenish colored solid.

This material is diluted with ethyl acetate and washed with water 2 x 50 ml). The aqueous washes are back-extracted with ethyl acetate and the combined organic extracts are dried (magnesium sulfate), filtered and concentrated to give 1.2 g of crude product mixture as a brown colored oil. This material is chromatographed over 50 g of silica gel (63-200$\mu$), eluting with 25% acetone/hexane and collecting 9 ml fractions. Fractions 38-60 are combined and concentrated to give 406 mg of slightly impure product. This material is subjected to a similar chromatographic sequence (5 ml fraction, 2% methanol/chloroform). Fractions 16-18 afford 98 mg of product contaminated with another unidentified component while fractions 19-23 afford 228 mg of pure 5-[$CH_3O[CH_2CH_2O]_5$]-1-Noa, Methyl Ester.

Physical characteristics are as follows:

$^1H$ NMR ($CDCl_3$) $\delta$ 7.94, 7.93, 7.40, 7.35, 6.87, 6.74, 4.82, 4.33-4.25, 4.03-3.95, 3.83, 3.85-3.76, 3.72-3.59, 3.56-3.50, 3.37; TLC (UV) R*f* = 0.46 in 3% methanol/chloroform.

F. A solution of 228 mg of 5-[$CH_3O[CH_2CH_2O]_5$]-1-Noa, methyl ester in 3.5 ml of methanol, 1 ml of water and 1 ml of 1.00 N sodium hydroxide is let stir at room temperature for 20 h. The reaction is neutralized with 0.1 N hydrochloric acid solution, diluted with methanol and then concentrated under reduced pressure to give the crude titled product as a dark brown oil.

Physical characteristics are as follows:

TLC (UV) R*f* = 0.00 in 3% methanol/chloroform. This material was used as is in subsequent experiments without further characterization or purification.

PREPARATIONS 172-270 AND EXAMPLES 12-21

Using the chemical procedures, starting materials and reactants described above, or methods anlogous thereto, the following additional parent and final compounds of the present invention are or may be prepared:

(172) Nα-[(2S,4S,5S)-5-[N-[2-(3-Pyridinyl)ethenylcarbonyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-[2-(2-pyridinylamino)ethyl]-L-isoleucinamide; or 3Py CH=CHCO CVA Ile $NH(CH_2)_2NH$ 2Py.

HR FAB MS $[M+H]^+$ *m/z* 635.4302.

HIV-1 Protease ($K_I$, nM): 4.

(173) Nα-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-benzimidazolylmethyl)-L-isoleucinamide; or 2Py CO CVA Ile Amb).

HR FAB MS $[M+H]^+$ *m/z* 619.3983.

HIV-1 Protease ($K_I$, nM): 2.

(174) Nα-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-[(2-hydroxy-2-phenyl)ethyl]-L-isoleucinamide; or 2Py CO CVA Ile Hpa.

HR FAB MS $[M+H]^+$ *m/z* 609.4003.

HIV-1 Protease ($K_{I,\phi}$ nM): 8.1.

(175) Nα-[(2S,4S,5S)-5-[N-[2-(3-Pyridinyl)ethenylcarbonyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-benzimidazolylmethyl)-L-isoleucinamide; or 3Py CH=CHCO CVA Ile Amb.

HR FAB MS $[M+H]^+$ *m/z* 645.4138.

HIV-1 Protease ($K_I$, nM): <10.

(176) N-[(2S,4S,5S)-5-[N-[2-(3-Pyridinyl)ethenylcarbonyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-[(1S,2R)-2-hydroxy-1-indanyl]amine; or 3Py CH=CHCO CVA Ahi.

HR FAB MS $[M+H]^+$ *m/z* 534.3312.

HIV-1 Protease ($K_I$, nM): 1.

(177) Nα-[(2S,4S,5S)-5-[N-[(4-Pyridinyl)methoxycarbonyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-benzimidazolylmethyl)-L-isoleucinamide; or 4Poc CVA Ile Amb.

HR FAB MS $[M+H]^+$ *m/z* 649.4087.

HIV-1 Protease ($K_I$, nM): 28.3.

(178) Nα-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-[4-[(3-nitro-2-pyridinyl)amino]-2-butenyl]-L-isoleucinamide; or 2Py CO CVA Ile Npb.

HR FAB MS $[M+H]^+$ *m/z* 680.4135.

HIV-1 Protease ($K_I$, nM): 12.

(Example 12) (Nα-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-(O-phosphoryl)-2-isopropyl-1-oxohexyl]-N-(2-benzimidazolylmethyl)-L-isoleucinamide, trifluoroacetic acid salt; or 2Py CO CVP Ile Amb.

HR FAB MS $[M+H]^+$ *m/z* 699.3654.

HIV-1 Protease ($K_I$, nM): 567.

(179) Nα-[(2S,4S,5S)-5-[N-[(2-Pyridinyl)methoxycarbonyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-benzimidazolylmethyl)-L-isoleucinamide; or 2Poc CVA Ile Amb.

HR FAB MS $[M+H]^+$ *m/z* 649.4100.

CV-1 Assay (% Inhibition): 87% at 1.0 μM.

(180) Nα-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-[2-[(3-nitro-2-pyridinyl)amino]ethyl]-L-isoleucinamide; or 2Py CO CVA Ile Npe.

HR FAB MS $[M+H]^+$ *m/z* 654.3999.

HIV-1 Protease ($K_I$, nM): <5.

(181) Nα-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-[2-[(3-amino-2-pyridinyl)amino]ethyl]-L-isoleucinamide; or 2Py CO CVA Ile Ape.

HR FAB MS $[M+H]^+$ *m/z* 624.4245.

HIV-1 Protease ($K_I$, nM): 12.

(182) N-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-[4-[(3-nitro-2-pyridinyl)amino]-2-butenyl]amine; or 2Py CO CVA Npb.

HR FAB MS $[M+H]^+$ *m/z* 567.3333.

HIV-1 Protease ($K_I$, nM): >250.

(Example 13) N-[(2S,4S,5S)-5-[N-[2-(3-Pyridinyl)ethenylcarbonyl]amino]-6-cyclohexyl-4-(O-phosphoryl)-2-isopropyl-1-oxohexyl]-N-[(1S,2R)-2-hydroxy-1-indanyl]amine; or 3Py CH=CHCO CVP Ahi.

HR FAB MS $[M+Na]^+$ *m/z* 636.3001.

HIV-1 Protease ($K_I$, nM): >200.

(183) N-[(2S,4S,5S)-5-[N-[(3-Pyridinyl)methyoxycarbonyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-[(1S,2R)-2-hydroxy-1-indanyl]amine; or 3Poc CVA Ahi.

HR FAB MS $[M+H]^+$ *m/z* 538.3304.

HIV-1 Protease ($K_I$, nM): <10.

(184) 2-[(2-phenoxy)ethoxy]benzoyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Peb-CVD-Ile-Amp.

HR FAB MS $[M+H]^+$ *m/z* 731.4375.

HIV-1 Protease ($K_I$, nM): 52.6.

(185) 2-[(2-phenoxy)ethoxy]benzoyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Peb-CVD-Ile-Amb.

HR FAB MS $[M+H]^+$ *m/z* 770.4512

HIV-1 Protease ($K_I$, nM): 8.1.

(186) 2-[(2-phenoxy)ethoxy]benzoyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-*tert*-butylmethylamine; or Peb-CVD-Ile-Tma.

HR FAB MS $[M+H]^+$ *m/z* 710.4750.

HIV-1 Protease ($K_I$, nM): 810.

(187) 2-[(2-phenoxy)ethoxy]benzoyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-2-aminomethylbenzimidazole; or Peb-CVD-Amb.

HR FAB MS $[M+H]^+$ *m/z* 597.3939.

CV-1 Assay (% Inhibition): 71.0% at 10.0 μM.

(188) 4-methyl-2-[(2-phenoxy)ethoxy]benzoyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-

isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Mpb-CVD-Ile-Amb.
HR FAB MS $[M+H]^+$ *m/z* 784.4461.
HIV-1 Protease ($K_I$, nM): 48.

(189) 2-[(phenylthio)methoxy]benzoyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Ptb-CVD-Ile-Amb.
HR FAB MS $[M+H]^+$ *m/z* 772.4156.
HIV-1 Protease ($K_I$, nM): 5.5.

(190) 3-[(2-phenoxy)ethoxy]propionyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Pep-CVD-Ile-Amb.
HR FAB MS $[M+H]^+$ *m/z* 722.4510.
HIV-1 Protease ($K_I$, nM): 4.

(191) 2-[2-(2-(2-methoxy)ethoxy)ethoxy)ethoxy]benzoyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Mee-CVD-Ile-Amb.
HR FAB MS $[M+H]^+$ *m/z* 796.4871.
HIV-1 Protease ($K_I$, nM): 10.5.

(192) 2-[(2-methoxy)ethoxy]benzoyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Meb-CVD-Ile-Amb.
HIV-1 Protease ($K_I$, nM): 89.

(193) 2-[2-(2-methoxy)ethoxy)ethoxy]benzoyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Mtb-CVD-Ile-Amb.
HR FAB MS $[M+H]^+$ *m/z* 752.4613.
HIV-1 Protease ($K_I$, nM): 4.5.

(Example 14) 1-naphthoxyacetyl-O-phosphoryl-L-seryl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine, dipotassium salt; or Noa-O-$PO_3K_2$-Ser-CVA-Ile-Amp.
HR FAB MS $[M+H]^+$ *m/z* 902.3472.
HIV-1 Protease ($K_I$, nM): 41.

(194) *tert*-butyloxycarbonyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-threonyl-2-aminomethylpyridine; or Boc-CVA-Thr-Amp.
HR FAB MS $[M+H]^+$ *m/z* 563.3828.
HIV-1 Protease ($K_I$, nM): 120.

(195) *tert*-butyloxycarbonyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-seryl-2-aminomethylpyridine; or Boc-CVA-Ser-Amp.
HR FAB MS $[M+H]^+$ *m/z* 549.3671.

HIV-1 Protease ($K_I$, nM): 120.

(196) 1-naphthoxyacetyl-L-histidyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-threonyl-2-aminomethylpyridine; or Noa-His-CVA-Thr-Amp.
HR FAB MS $[M+H]^+$ *m/z* 784.4389.
HIV-1 Protease ($K_I$, nM): <5.

(197) 2-acetoxybenzoyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Acb-CVA-Ile-Amp.
HR FAB MS $[M+H]^+$ *m/z* 637.3934.
HIV-1 Protease ($K_I$, nM): 12.1.

(198) 1-naphthoxyacetyl-L-valyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-seryl-2-aminomethylpyridine; or Noa-Val-CVA-Ser-Amp.
HR FAB MS $[M+H]^+$ *m/z* 732.4320.
HIV-1 Protease ($K_I$, nM): 8.1.

(199) 1-naphthoxyacetyl-L-valyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-threonyl-2-aminomethylpyridine; or Noa-Val-CVA-Thr-Amp.
HR FAB MS $[M+H]^+$ *m/z* 746.4491.
HIV-1 Protease ($K_I$, nM): 10.

(200) 1-naphthoxyacetyl-L-threonyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Noa-Thr-CVA-Ile-Amp.
HR FAB MS $[M+H]^+$ *m/z* 760.4661.
HIV-1 Protease ($K_I$, nM): <10.

(201) 1-naphthoxyacetyl-L-seryl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Noa-Ser-CVA-Ile-Amp.
HR FAB MS $[M+H]^+$ *m/z* 746.4519.
HIV-1 Protease ($K_I$, nM): <10.

(202) 2-hydroxybenzoyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Hyb-CVA-Ile-Amp.
HR FAB MS $[M+H]^+$ *m/z* 595.3830.
HIV-1 Protease ($K_I$, nM): 158.

(203) methoxycarbonyl-D-prolyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Moc-D-Pro-CVA-Ile-Amp.
HR FAB MS $[M+H]^+$ *m/z* 630.4219.
HIV-1 Protease ($K_I$, nM): 89.

(204) *tert*-butyloxycarbonyl-L-prolyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Boc-Pro-CVA-Ile-Amp.

HR FAB MS $[M+H]^+$ *m/z* 672.4727.

HIV-1 Protease ($K_I$, nM): 73.

(205) methoxycarbonyl-L-prolyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Moc-Pro-CVA-Ile-Amp.

HR FAB MS $[M+H]^+$ *m/z* 630.4219.

HIV-1 Protease ($K_I$, nM): 308.

(206) Acetyl-L-prolyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Ac-Pro-CVA-Ile-Amp.

HR FAB MS $[M+H]^+$ *m/z* 614.4289.

HIV-1 Protease ($K_I$, nM): 146.

(207) 1-naphthoxyacetyl-L-histidyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-1S-amino-2R-hydroxy-indane; or Noa-His-CVA-Ahi.

HR FAB MS $[M+H]^+$ *m/z* 724.4110.

HIV-1 Protease ($K_I$, nM): 40.

(208) 1-naphthoxyacetyl-L-histidyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-1S-amino-2R-hydroxy-indane; or Noa-His-CVD-Ahi.

HR FAB MS $[M+H]^+$ *m/z* 740.4029.

HIV-1 Protease ($K_I$, nM): 14.2.

(209) 1-naphthoxyacetyl-L-threonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Noa-Thr-CVD-Ile-Amb.

HR FAB MS $[M+H]^+$ *m/z* 815.4704.

HIV-1 Protease ($K_I$, nM): $<5$.

(210) 1-naphthoxyacetyl-L-seryl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Noa-Ser-CVD-Ile-Amb.

HR FAB MS $[M+H]^+$ *m/z* 801.4573.

HIV-1 Protease ($K_I$, nM): 28.9.

(211) 1-naphthoxyacetyl-L-homoseryl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Noa-Hsr-CVA-Ile-Amp.

HR FAB MS $[M+H]^+$ *m/z* 760.4661.

HIV-1 Protease ($K_I$, nM): 15.

(212) 1-naphthoxyacetyl-L-threonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-1S-amino-2R-hydroxy-indane; or Noa-Thr-CVD-Ahi.

HR FAB MS $[M+H]^+$ *m/z* 704.3913.

CV-1 Assay (% Inhibition): 78.0% at 1.0 $\mu$M.

(213) 1-naphthoxyacetyl-L-seryl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-1S-amino-2R-hydroxy-indane; or Noa-Ser-CVD-Ahi.

HR FAB MS $[M+H]^+$ *m/z* 690.3778.

HIV-1 Protease ($K_I$, nM): 30.

(214) 1-naphthoxyacetyl-$L_s$-histidyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-1S-amino-2R-hydroxy-indane; or Noa-His-CVD-Ahi.

HR FAB MS $[M+H]^+$ *m/z* 740.4029.

(215) 4-morpholinecarbonyl-L-valyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Morph-Val-CVA-Ile-Amp.

HR FAB MS $[M+H]^+$ *m/z* 686.4731.

HIV-1 Protease ($K_I$, nM): 11.3.

(216) acetyl-L-valyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Acetyl-Val-CVA-Ile-Amp.

HR FAB MS $[M+H]^+$ *m/z* 615.4359.

CV-1 Assay (% Inhibition): 72.0% at 1.0 $\mu$M.

(217) 1-naphthoxyacetyl-$N^{\alpha}$methyl-L-histidyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Noa-$N^{\alpha}$methyl-His-CVA-Ile-Amp.

HR FAB MS $[M+H]^+$ *m/z* 809.4840.

CV-1 Assay (% Inhibition): 60.0% at 1.0 $\mu$M.

(218) 3-(4-hydroxyphenyl)-butyryl-L-histidyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Dat-His-CVA-Ile-Amp.

HR FAB MS $[M+H]^+$ *m/z* 759.4683.

HIV-1 Protease ($K_I$, nM): $<10$.

(219) 5-OH-1-naphthoxyacetyl-L-histidyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or 5-OH-NOA-His-CVA-Ile-Amp.

HR FAB MS $[M+H]^+$ *m/z* 811.4632.

CV-1 Assay (% Inhibition): 53.0% at 1.0 $\mu$M.

(220) 2-[(2-phenoxy)ethoxy]benzoyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Peb-CVA-Ile-Amb.

HR FAB MS $[M+H]^+$ *m/z* 754.4543.

HIV-1 Protease ($K_I$, nM): 20.2.

(221) 3-(4-hydroxyphenyl)-butyryl-L-valyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Dat-Val-CVA-Ile-Amb.

HR FAB MS $[M+H]^+$ *m/z* 760.4887.

HIV-1 Protease ($K_I$, nM): 40.5.

(222) hydroxyacetyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Hydroxyacetyl-CVA-Ile-Amb.

HR FAB MS $[M+H]^+$ *m/z* 571.3733.

HIV-1 Protease ($K_{I,}$ nM): 11.7.

(223) 2-hydroxy-3-methylbutryl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Hmb-CVA-Ile-Amb (less polar isomer).

HR FAB MS $[M+H]^+$ *m/z* 613.4203.

HIV-1 Protease ($K_I$, nM): 70.

(224) 2-hydroxy-3-methylbutryl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Hmb-CVA-Ile-Amb (more polar isomer).

HR FAB MS $[M+H]^+$ *m/z* 613.4203.

HIV-1 Protease ($K_I$, nM): 34.

(225) 3-(4-hydroxyphenyl)-butyryl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Dat-CVA-Ile-Amp.

HR FAB MS $[M+H]^+$ *m/z* 622.4094.

HIV-1 Protease ($K_I$, nM): 22.3.

(226) 4-hydroxyphenylacetyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or 4-Hpa-CVA-Ile-Amb.

HR FAB MS $[M+H]^+$ *m/z* 647.4046.

HIV-1 Protease ($K_I$, nM): $<10$.

(227) 2-hydroxyphenylacetyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or 2-Hpa-CVA-Ile-Amb.

HR FAB MS $[M+H]^+$ *m/z* 647.4046.

HIV-1 Protease ($K_I$, nM): 8.1.

(228) 3-hydroxyphenylacetyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or 3-Hpa-CVA-Ile-Amb.

HR FAB MS $[M+H]^+$ *m/z* 647.4046.

HIV-1 Protease ($K_I$, nM): $<10$.

(229) 3-(4-hydroxyphenyl)-butyryl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Dat-CVA-Ile-Amb.

HR FAB MS $[M+H]^+$ *m/z* 661.4203.

HIV-1 Protease ($K_I$, nM): 4.

(230) 3-(4-hydroxyphenyl)-butyryl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-1S-amino-2R-hydroxy-indane; or Dat-CVD-Ahi.

HR FAB MS $[M+H]^+$ *m/z* 665.4040.

(231) 1-naphthylenyloxyacetyl-L-asparaginyl-5*S*-amino-6-cyclohexyl-4*S*hydroxy-2*S*-isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine; or Noa-Asn-CVA-Ile-Amp.

$C_{43}H_{60}N_6O_7$ $[M+H]^+$ = 773.

HIV-1 Protease ($K_I$, nM): 4.

(232) ((5-(3,6,9-trioxa-dec-1-yl)oxy)naphthalen-1-yl)oxyacetyl-L-asparaginyl-5*S*-amino-6-cyclohexyl-4*S*-hydroxy-2*S*-isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine; or 5-Trieg-Noa-Asn-CVA-Ile-Amp.

$C_{50}H_{74}N_6O_{11}$ $[M+H]^+$ = 935.5476.

HIV-1 Protease ($K_I$, nM): 32.4.

(233) ((4-(3,6,9-trioxa-dec-1-yl)oxy)naphthalen-1-yl)oxyacetyl-L-asparaginyl-5*S*-amino-6-cyclohexyl-4*S*-hydroxy-2*S*-isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine; or 4-Trieg-Noa-Asn-CVA-Ile-Amp.

$C_{50}H_{74}N_6O_{11}$ $[M+H]^+$ = 935.5494.

HIV-1 Protease ($K_I$, nM): 14.2.

(234) 1-naphthalenyloxyacetyl-L-valinyl-5*S*-amino-6-cyclohexyl-4*S*-hydroxy2*S*-isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine; or Noa-Val-CVA-Ile-Amp.

$C_{44}H_{63}N_5O_6$ $[M+H]^+$ = 758.4839.

CV-1 Assay (% Inhibition): 93.0% at 10.0 $\mu$M.

(235) ((5-(3,6,9-trioxa-dec-1-yl)oxy)naphthalen-1-yl)oxyacetyl-L-asparaginyl-5*S*-amino-6-cyclohexyl-4*S*-hydroxy-2*S*-isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine; or 5-Trieg-Noa-His-CVA-Ile-Amp.

$C_{52}H_{75}N_7O_{10}$ $[M+H]^+$ = 958.5629.

HIV-1 Protease ($K_I$, nM): 6.3.

(236) ((5-(3,6,9-trioxa-dec-1-yl)oxy)naphthalen-1-yl)oxyacetyl-L-asparaginyl-5*S*-amino-6-cyclohexyl-4*S*-hydroxy-2*S*-isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine; or 4-Trieg-Noa-His-CVA-Ile-Amp.

$C_{52}H_{75}N_7O_{10}$ $[M+H]^+$ = 958.5653.

HIV-1 Protease ($K_I$, nM): 6.7.

(237) ((5-(3,6,9-trioxa-dec-1-yl)oxy)naphthal-1-yl)oxyacetyl-L-valinyl-5*S*amino-6-cyclohexyl-4*S*-hydroxy-2*S*-isopropyl-hexanoyl-L-isoleucinyl-2aminomethylpyridine; or 5-Trieg-Noa-Val-CVA-Ile-Amp.

$C_{51}H_{77}N_5O_{10}$ $[M+H]^+$ = 920.5748.

HIV-1 Protease ($K_I$, nM): 40.

(238) ((4-(3,6,9-trioxa-dec-1-yl)oxy)naphthalen-1-yl)oxyacetyl-L-valinyl5*S*-amino-6-cyclohexyl-4*S*-hydroxy-2*S*-isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine; or 4-Trieg-Noa-Val-CVA-Ile-Amp.

$C_{51}H_{77}N_5O_{10}$ $[M+H]^+$ = 920.5749.

HIV-1 Protease ($K_I$, nM): $< 10$.

(239) ((5-(3,6,9,12,15-pentaoxa-hexadec-1-yl)oxy)naphthalen-1yl)oxyacetyl-L-histidinyl-5*S*-amino-6-cyclohexyl-4*S*-hydroxy-2*S*isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine; or 5-Pentaeg-Noa-His-CVA-Ile-Amp.

$C_{56}H_{83}N_7O_{12}$ $[M+H]^+ = 1046$.

HIV-1 Protease ($K_I$, nM): 10.5.

(240) ((5-(3,6,9,12,15,18-hexaoxa-nonadec-1-yl)oxy)naphthalen-1yl)oxyacetyl-L-histidinyl-5*S*-amino-6-cyclohexyl-4*S*-hydroxy-2*S*isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine; or 5-Hexaeg-Noa-His-CVA-Ile-Amp.

$C_{58}H_{87}N_7O_{13}$ $[M+H]^+ = 1090.6438$.

HIV-1 Protease ($K_I$, nM): 12.

(241) ((5-(3,6,9,12,15-pentaoxa-hexadec-1-yl)oxy)naphthalen-1yl)oxyacetyl-L-histidinyl-5*S*-amino-6-cyclohexyl-3*R*,4*R*-dihydroxy-2*R*isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine; or 5-Pentaeg-Noa-His-CVD-Ile-Amp.

$C_{56}H_{83}N_7O_{13}$ $[M+H]^+ = 1062.6082$.

HIV-1 Protease ($K_I$, nM): 7.7.

(242) 2-((3-(4-(3,6,9-trioxadec-1-yloxy)phenyl)prop-1-yl)oxy)benzoyl-5*S*amino-6-cyclohexyl-3*R*,4*R*-dihydroxy-2*R*-isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine.

$C_{50}H_{74}N_4O_{10}$ $[M+H]^+ = 891.5507$.

HIV-1 Protease ($K_I$, nM): 142.

(243) ((5-(8-amino-3,6-dioxa-oct-1-yl)oxy)naphthalen-1-yl)oxyacetyl-L-valinyl-5*S*-amino-6-cyclohexyl-3*R*,4*R*-dihydroxy-2*R*-isopropylhexanoyl-L-isoleucinyl-2-aminomethylpyridine.

$C_{50}H_{76}N_6O_{10}$ $[M+H]^+ = 921.5695$.

CV-1 Assay (% Inhibition): 80.0% at 1.0 $\mu$M.

(244) ((5-(8-trimethylamminyl-3,6-dioxa-oct-1-yl)oxy)naphthalen-1yl)oxyacetyl-L-valinyl-5*S*-amino-6-cyclohexyl-3*R*,4*R*-dihydroxy-2*R*isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine iodide.

$C_{53}H_{83}I_1N_6O_{10}$ $[M-I]^+ = 963.6188$.

HIV-1 Protease ($K_I$, nM): $< 10$.

(245) ((5-(3,6,9,12,15-pentaoxa-hexadec-1-yl)oxy)naphthalen-1yl)oxyacetyl-L-valinyl-5*S*-amino-6-cyclohexyl-3*R*,4*R*-dihydroxy-2*R*isopropyl-hexanoyl-L-isoleucinyl-1*S*-amino-2*R*-hydroxy-indane; or 5-PentaegNoa-Val-CVD-Ile-Ahi.

$C_{52}H_{78}N_3O_{13}$ $[M+H]^+ = 952.5532$.

(246) naphthalene-2-sulfonyl-L-histidinyl-5*S*-amino-6-cyclohexyl-4*S*hydroxy-2*S*-isopropyl-

hexanoyl-L-isoleucinyl-2-aminomethylpyridine.

$C_{43}H_{59}N_7O_6S_1$ $[M+H]^+ = 802.4320$.

HIV-1 Protease ($K_I$,nM): 36.4.

(247) 2-[(2-phenoxy)ethoxy]benzoyl-5*S*-amino-6-cyclohexyl-3*R*,4*R*-dihydroxy2*R*-isopropyl-hexanoyl-L-isoleucinyl-1-aminoethyl(4-methylthiazole).

$C_{42}H_{60}N_4O_7S_1$ $[M+H]^+ = 765$.

HIV-1 Protease ($K_I$, nM): 65.

(248) 2-(2-(4-methylthiazol-5-yl)ethyl)oxy)benzoyl-5*S*-amino-6-cyclohexyl3*R*,4*R*-dihydroxy-2*R*-isopropyl-hexanoyl-L-isoleucinyl-2aminomethylpyridine.

$C_{40}H_{57}N_5O_6S_1$ $[M+H]^+ = 736$.

HIV-1 Protease ($K_I$, nM): 9.1.

(249) 2-(2-(4-methylthiazol-5-yl)ethyl)thio)benzoyl-5*S*-amino-6cyclohexyl-3*R*,4*R*-dihydroxy-2*R*-isopropyl-hexanoyl-L-isoleucinyl-2aminomethylpyridine.

$C_{40}H_{57}N_5O_5S_2$ $[M+H]^+ = 752$.

HIV-1 Protease ($K_I$, nM): 5.1.

(250) 2-(2-(4-methylthiazol-5-yl)ethyl)oxy)benzoyl-5*S*-amino-6-cyclohexyl3*R*,4*R*-dihydroxy-2*R*-isopropyl-hexanoyl-L-isoleucinyl-1-aminoethyl(4methylthiazole).

$C_{40}H_{59}N_5O_6S_2$ $[M+H]^+ = 770$.

HIV-1 Protease ($K_I$, nM): 49.6.

(251) 2-(2-(4-methylthiazol-5-yl)ethyl)thiyl)benzoyl-5*S*-amino-6cyclohexyl-3*R*,4*R*-dihydroxy-2*R*-isopropyl-hexanoyl-L-isoleucinyl 1aminoethyl(4-methylthiazole).

$C_{40}H_{59}N_5O_5S_3$ $[M+H]^+ = 786$.

HIV-1 Protease ($K_I$, nM): 15.7.

(252) 2-((4-([3a*S*-(3aα,4β,6aα)]-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-on-4yl)pent-1-yl)thio)benzoyl-5*S*-amino-6-cyclohexyl-3*R*,4*R*-dihydroxy-2*R*isopropyl-hexanoyl-L-isoleucinyl-amino-2-(4-methylthiazol-5yl)ethane.

$C_{44}H_{68}N_6O_6S_3$ $[M+H]^+ = 873$.

HIV-1 Protease ($K_I$, nM): 4.

(253) 2-((4-([3a*S*-(3aα,4β,6aα)]-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-on-4yl)pent-1-yl)oxy)benzoyl-5*S*-amino-6-cyclohexyl-3*R*,4*R*-dihydroxy-2*R*isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine.

$C_{44}H_{66}N_6O_7S_1$ $[M+H]^+ = 823$.

HIV-1 Protease ($K_I$, nM): 10.4.

(254) 4-([3a*S*-((3aα,4β,6aα)]-1*H*-thieno[3,4-*d*]imidazolyl)pentanoyl-5*S*amino-6-cyclohexyl-3*R*,4*R*-dihydroxy-2*R*-isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine; or

Biotinoyl-CVD-Ile-AMP.

$C_{37}H_{60}N_6O_6S_1$ $[M+H]^+ = 717$.

HIV-1 Protease ($K_I$, nM): 44.5.

(255) 4-([3a*S*-(3aα,4β,6aα)]-1*H*-thieno[3,4-*d*]imidazolyl)pentanoyl-L-valinyl-5*S*-amino-6-cyclohexyl-3*R*,4*R*-dihydroxy-2*R*-isopropylhexanoyl-L-isoleucinyl-2-aminomethylpyridine; or Biotinoyl-Val-CVD-Ile-AMP.

$C_{42}H_{69}N_7O_7S_1$ $[M+H]^+ = 816$.

HIV-1 Protease ($K_I$, nM): <4.

(256) 4-([3a*S*-(3aα,4β,6aα)]-1*H*-thieno[3,4-*d*]imidazolyl)pentanoyl-6aminohexanoyl-5*S*-amino-6-cyclohexyl-3*R*,4*R*-dihydroxy-2*R*-isopropylhexanoyl-L-isoleucinyl-2-aminomethylpyridine; or Biotinoyl-Aminohexanoyl-CVD-Ile-AMP.

$C_{43}H_{71}N_7O_7S_1$ $[M+H]^+ = 830$.

HIV-1 Protease ($K_I$, nM): 20.2.

(257) naphthalene-2-sulfonyl-L-valinyl-5*S*-amino-2*S*-benzyl-3*R*,4*R*-dihydroxy7-methyl-octanoyl-L-isoleucinyl-2-aminomethylpyridine.

$C_{43}H_{57}N_5O_7S_1$ $[M+H]^+ = 788$.

HIV-1 Protease ($K_I$, nM): 4.

(258) 1-naphthyloxyacetyl-L-histidinyl-5*S*-amino-2*S*-benzyl-3*R*,4*R*-dihydroxy7-methyl-octanoyl-L-isoleucinyl-2-aminomethylpyridine; or Noa-His-LFD-Ile-Amp.

$C_{46}H_{57}N_7O_7$ $[M+H]^+ = 820$.

HIV-1 Protease ($K_I$, nM): 28.

(259) 2-[(2-phenoxy)ethoxy]benzoyl-5*S*-amino-2*S*-benzyl-3*R*,4*R*-dihydroxy-7methyl-octanoyl-L-isoleucinyl-2-aminomethylpyridine; or Pep-LFD-Ile-Amp.

$C_{43}H_{54}N_4O_7$ $[M+H]^+ = 739$.

HIV-1 Protease ($K_I$, nM): 186.

(260) 2-[(2-phenoxy)ethoxy]benzoyl-5*S*-amino-2*S*-benzyl-3*R*,4*R*-dihydroxy-7methyl-octanoyl-L-isoleucinyl-amino-2-(4-methylthiazol-5-yl)ethane.

$C_{42}H_{60}N_4O_7S_1$ $[M+H]^+ = 765$.

HIV-1 Protease ($K_I$, nM): 65.

(261) naphthalene-2-sulfonyl-L-asparaginyl-5*S*-amino-2*S*-benzyl-3*R*,4*R*dihydroxy-7-methyl-octanoyl-L-isoleucinyl-2-aminomethylpyridine.

$C_{42}H_{54}N_6O_8S_1$ $[M+H]^+ = 803$.

HIV-1 Protease ($K_I$, nM): 40.5

(262) naphthalene-2-sulfonyl-L-valinyl-5*S*-amino-2*S*-((2-phenyl)eth-1-yl)3*R*,4*R*-dihydroxy-7-methyl-octanoyl-L-isoleucinyl-2aminomethylpyridine.

$C_{44}H_{59}N_5O_7S_1$ $[M+H]^+ = 802$.

CV-1 Assay (% Inhibition): 50.0% at 1.0 $\mu$M.

(263) naphthalene-2-sulfonyl-L-leucinyl-5*S*-amino-2*S*-benzyl-3*R*,4*R*dihydroxy-7-methyl-octanoyl-L-isoleucinyl-2-aminomethylpyridine.

$C_{44}H_{59}N_5O_7S_1$ $[M+H]^+ = 802$.

HIV-1 Protease ($K_I$, nM): 10.1.

(264) 2-[(2-phenoxy)ethoxy]benzoyl-5*S*-amino-2*S*-benzyl-3*R*,4*R*-dihydroxy-7methyl-octanoyl-L-isoleucinyl-2-aminomethylbenzimidazole; or Pep-LFD-Ile-Amb.

$C_{45}H_{55}N_5O_7$ $[M+H]^+ = 778$.

HIV-1 Protease ($K_I$, nM): 40.

(265) 2-((3-(4-(3,6,9-trioxadec-1-yloxy)phenyl)prop-1-yl)oxy)benzoyl-5*S*amino-2*S*-benzyl-3*R*,4*R*-dihydroxy-7-methyl-octanoyl-1*S*-amino-2*R*hydroxy-indane.

$C_{48}H_{62}N_2O_{10}$ $[M+H]^+ = 827$.

HIV-1 Protease ($K_I$, nM): 77.

(266) Nα-[(2S,4S,5S)-5-[N-[2-[2-[2-(2-Methoxyethoxy)ethoxy]ethoxy]phenylcarbonyl] amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-benzimidazolylmethyl)-L-isoleucinamide; or Mee CVA Ile Amb.

HR FAB MS $[M+H]^+$ *m/z* 780.4922.

HIV-1 Protease ($K_I$, nM): 8.1.

(Example 15) Nα-[(2S,4S,5S)-5-[N-[2-[2-[22-(2-methoxyethoxy)ethoxy]ethoxy] phenylcarbonyl]-amino-6-cyclohexyl-4-(O-phosphoryl)-2-isopropyl-1-oxohexyl]-N-(2-benzimidazolylmethyl)-L-isoleucinamide; or Mee CVP Ile Amb.

(267) (1-naphthoxy)acetyl-L-threonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Noa-Thr-CVD-Ile-Amp.

(268) ((5-(3,6,9,12,15-pentaoxa-hexdec-1-yl)oxy)naphthalen-1-yl)oxyacetyl-L-threonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or 5-PentaegNoa-Thr-CVD-Ile-Amp.

(269) ((5-(3,6,9,12,15-pentaoxa-hexdec-1-yl)oxy)naphthalen-1-yl)oxyacetyl-L-threonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or 5-PentaegNoa-Thr-CVD-Ile-Amb.

(270) ((5-(3,6,9,12,15-pentaoxa-hexdec-1-yl)oxy)naphthalen-1-yl)oxyacetyl-L-threonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-1S-amino-2R-hydroxy-indane; or 5-PentaegNoa-Thr-CVD-Ahi.

(Example 16) ((5-(3,6,9,12,15-pentaoxa-hexdec-1-yl)oxy)naphthalen-1-yl)oxyacetyl-O-phosphoryl-L-threonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine, dipotassium salt; or 5-

PentaegNoa-$OPO_3K_2$-Thr-CVD-Ile-Amp.

(Example 17) ((5-(3,6,9,12,15-pentaoxa-hexdec-1-yl)oxy)naphthalen-1-yl)oxyacetyl-O-phosphoryl-L-threonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole, dipotassium salt; or 5-PentaegNoa-$OPO_3K_2$-Thr-CVD-Ile-Amb.

(Example 18) ((5-(3,6,9,12,15-pentaoxa-hexdec-1-yl)oxy)naphthalen-1-yl)oxyacetyl-O-phosphoryl-L-threonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-1S-amino-2R-hydroxy-indane, dipotassium salt; or 5-PentaegNoa-$OPO_3K_2$-Thr-CVD-Ahi.

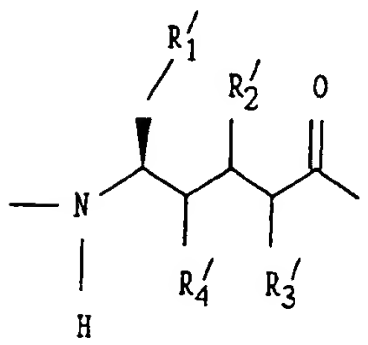
(Example 19) (1-naphthoxy)acetyl-O-phosphoryl-L-threonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine, dipotassium salt; or Noa-$OPO_3K_2$-Thr-CVD-Ile-Amp.

(Example 20) (1-naphthoxy)acetyl-O-phosphoryl-L-threonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole, dipotassium salt; or Noa-$OPO_3K_2$-Thr-CVD-Ile-Amb.

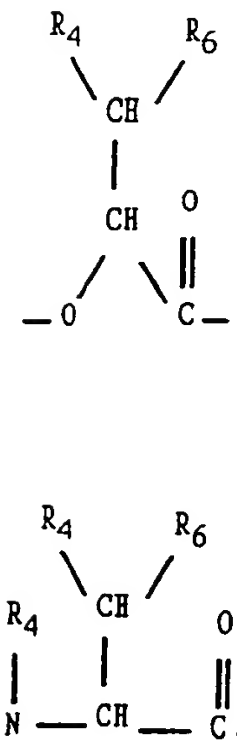
(Example 21) (1-naphthoxy)acetyl-O-phosphoryl-L-threonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-1S-amino-2R-hydroxy-indane, dipotassium salt; or Noa-$OPO_3K_2$-Thr-CVD-Ahi.

STRUCTURE CHART

$X_1$-$C_8$-$D_9$-$E_{10}$-$F_{11}$-$G_{12}$-Z I



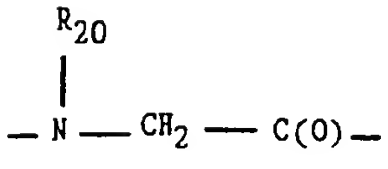
X



$XL_1$

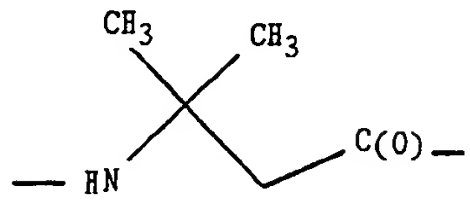


$XL_2$

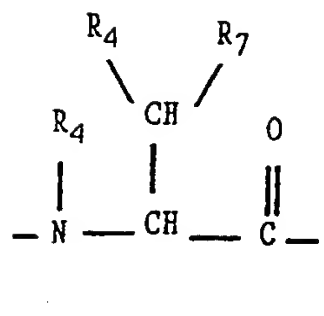


$XL_{2a}$

STRUCTURE CHART (continued)



$XL_{2b}$



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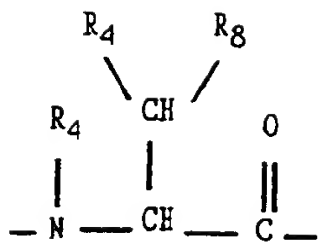

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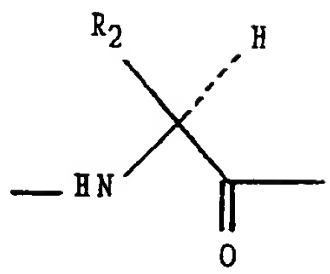
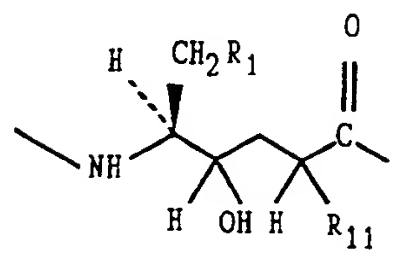


$XL_{4a}$

STRUCTURE CHART (continued)



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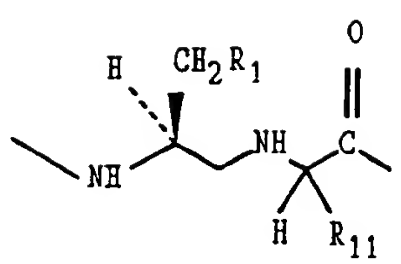
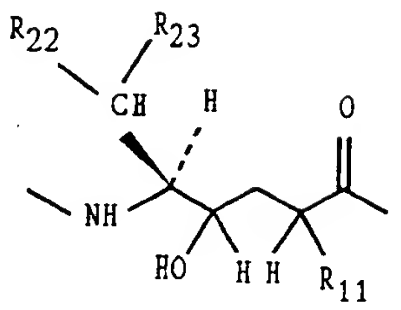
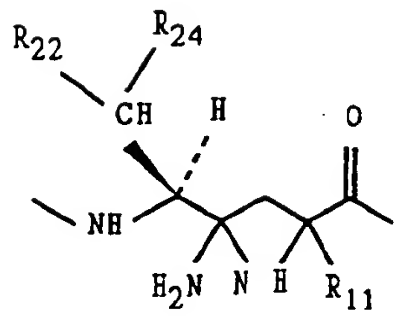


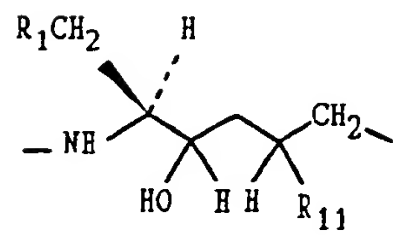
$XL_{6b}$



$XL_{6c}$

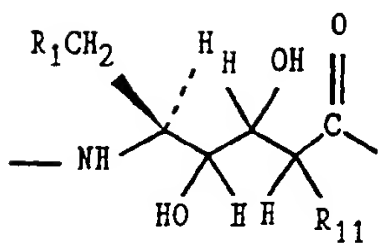


$XL_{6d}$

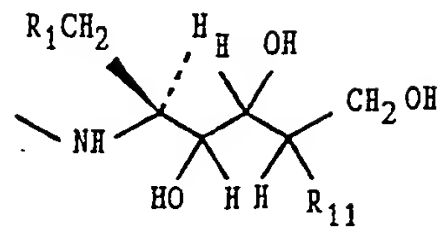


$XL_{6e}$

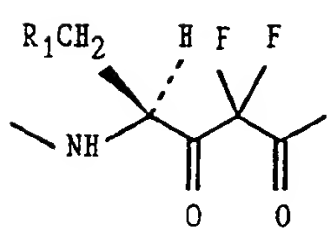
STRUCTURE CHART (continued)



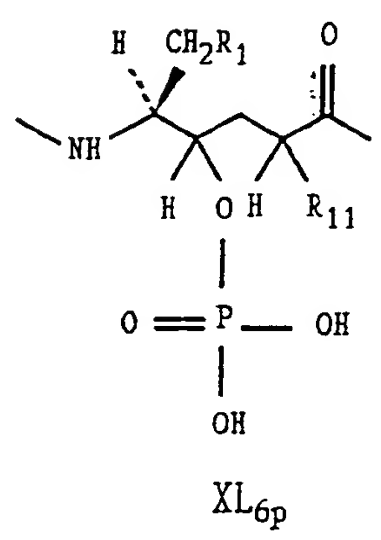
II



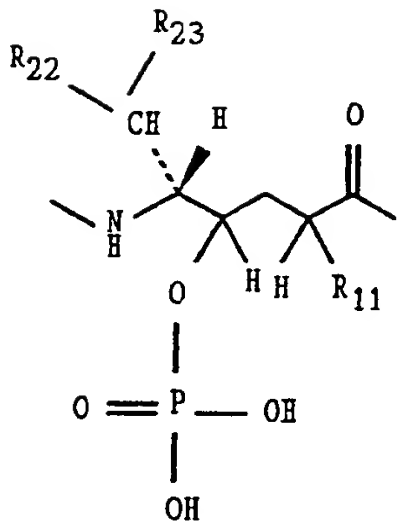
III



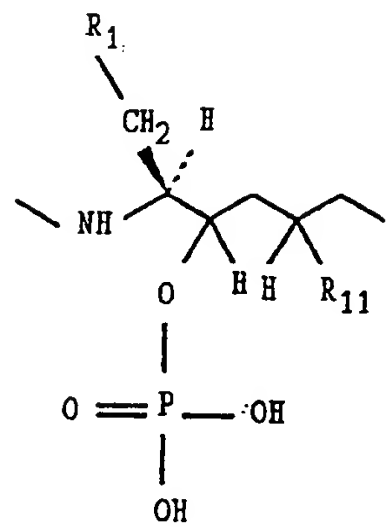
IV



$XL_{6p}$

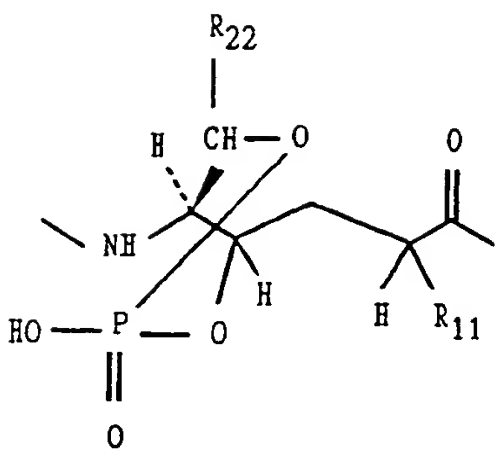


$XL_{6cp}$

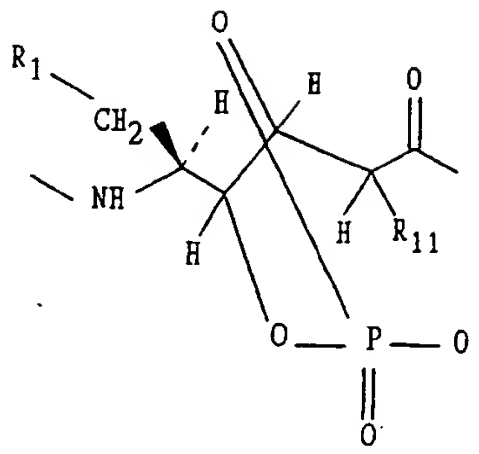


$XL_{6ep}$

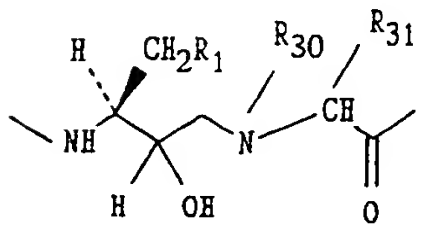
STRUCTURE CHART (continued)



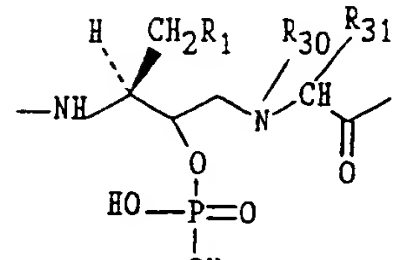
$XL_{6ccp}$



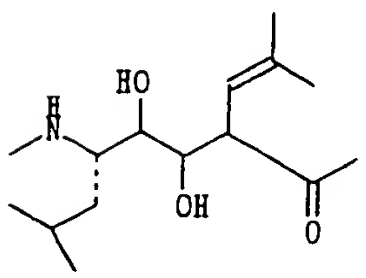
$II_{cp}$



V



Vp



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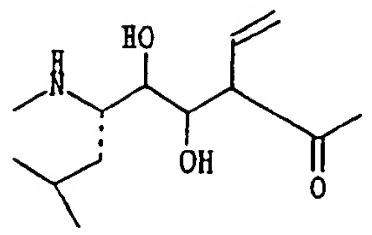
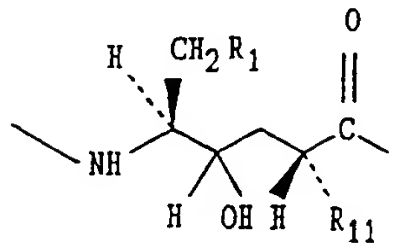
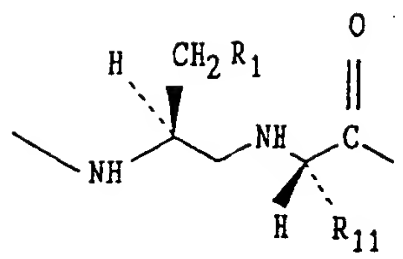


VII

STRUCTURE CHART (continued)



$XL_6$



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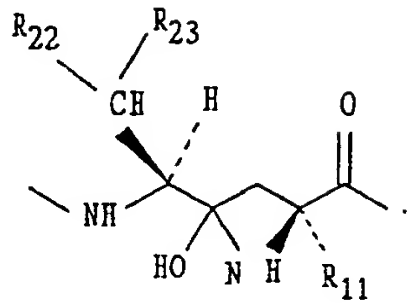

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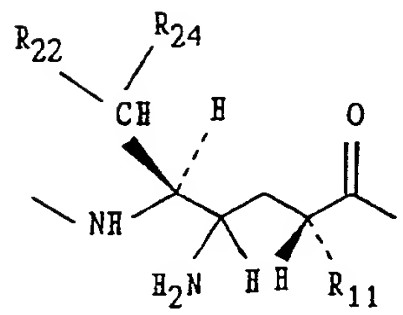

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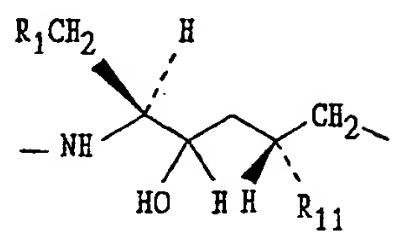

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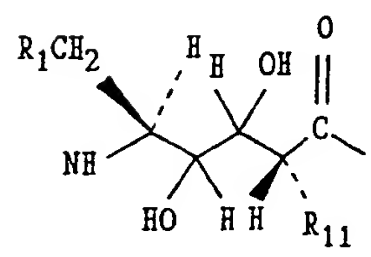
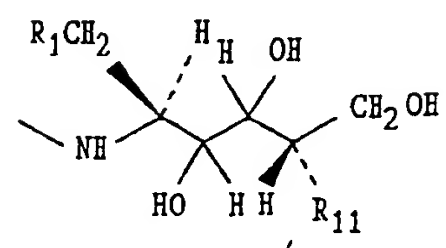
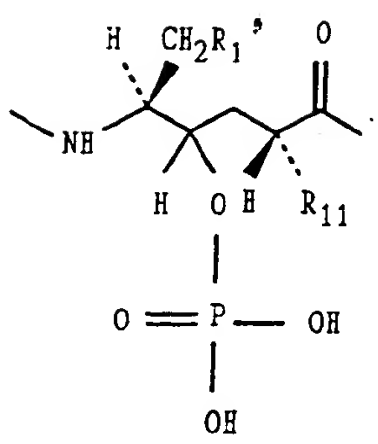


II



III

STRUCTURE CHART (continued)



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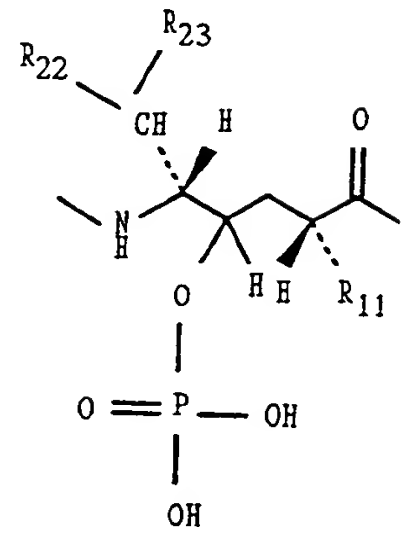
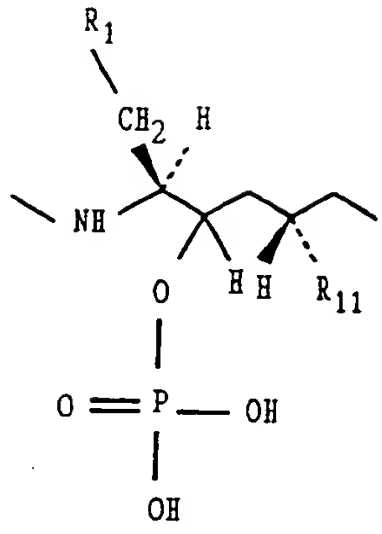


$XL_{6cp}$



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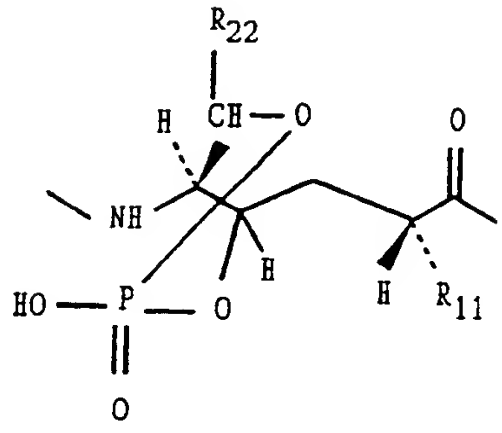

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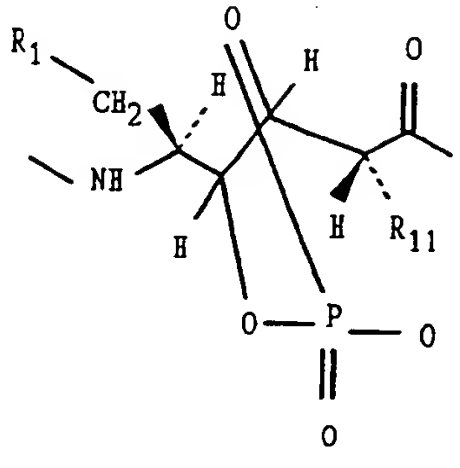
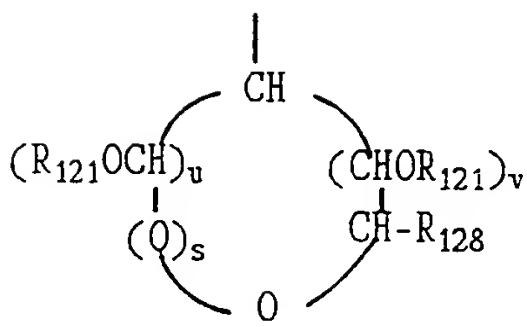
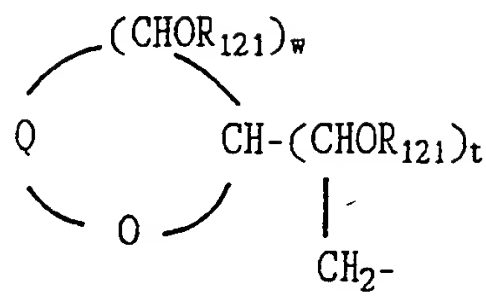


$II_{cp}$

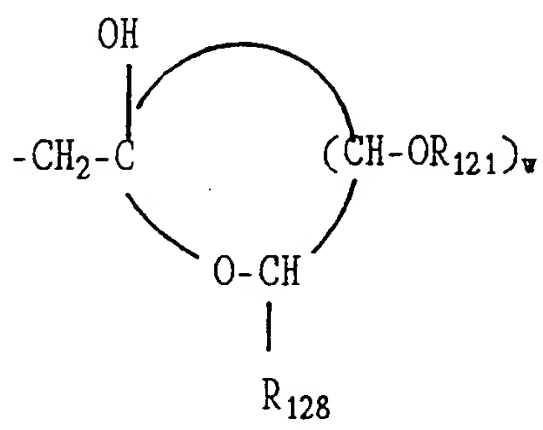
STRUCTURE CHART (continued)



XXX



XXXI

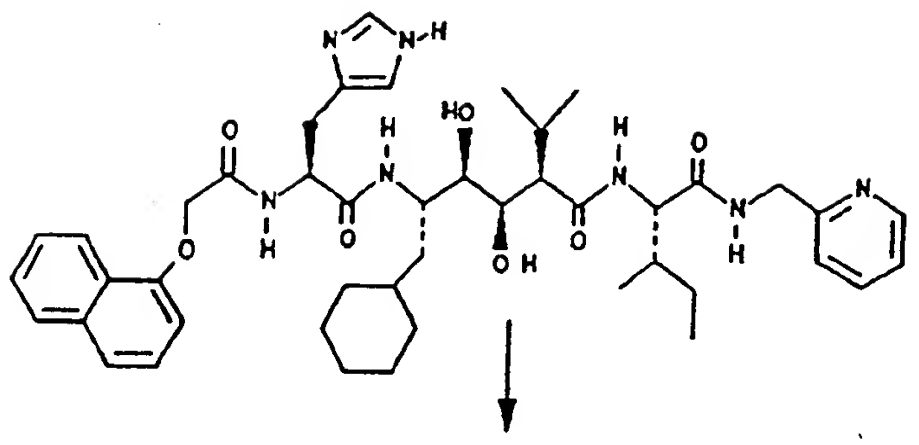


XXXII

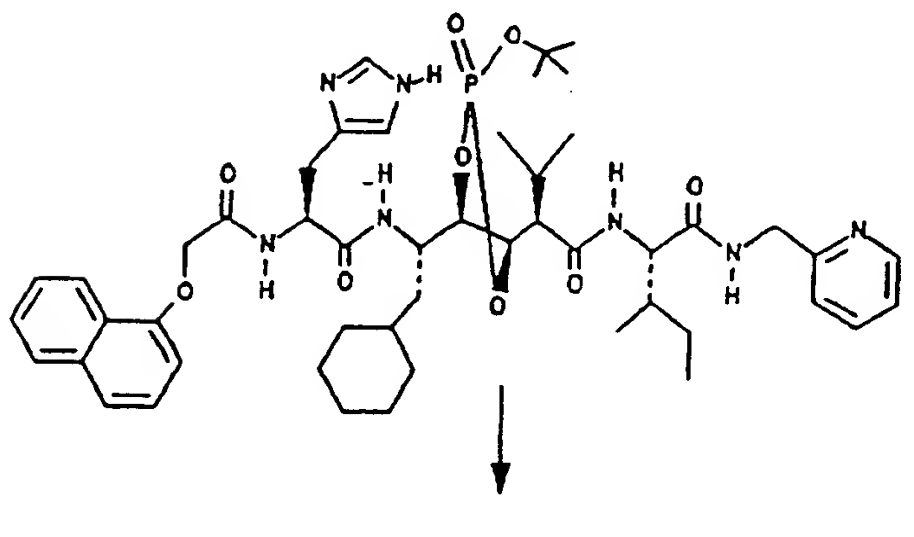
$$e(\%) = B(\%) + \frac{(t-2t_o-X)}{y} \times A\ (\%) \quad \text{Equation Q}$$

$$e(\%) = 17 + \frac{(12.63-2.4-2)}{20} \times 83 \quad \text{Equation U}$$

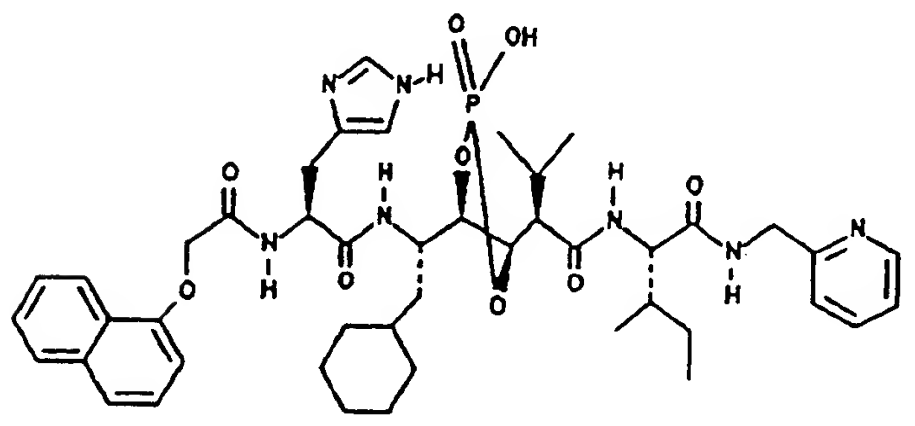
CHART A



A-1

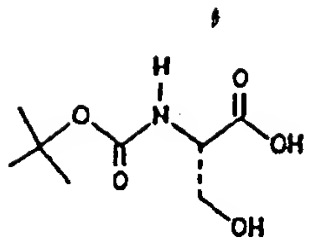


A-2

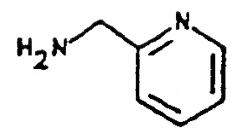


A-3

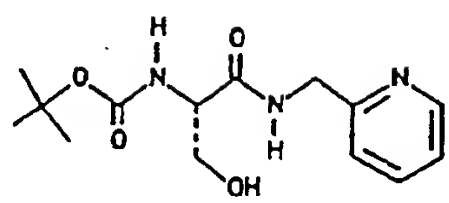
CHART B



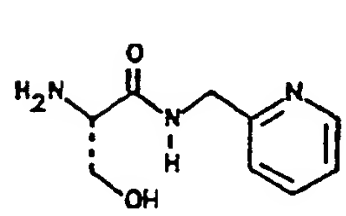
B-1



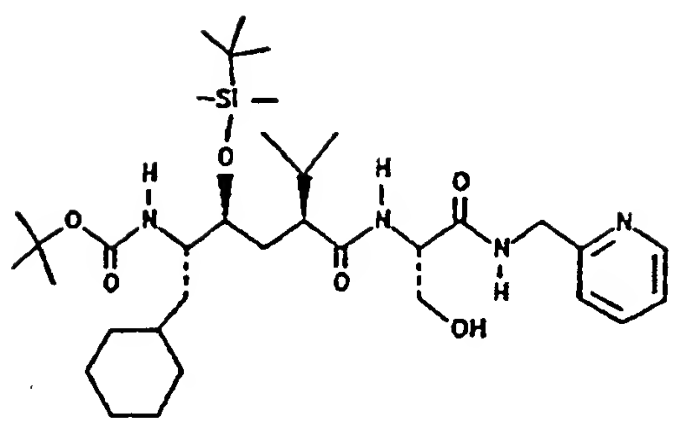
B-2



B-3

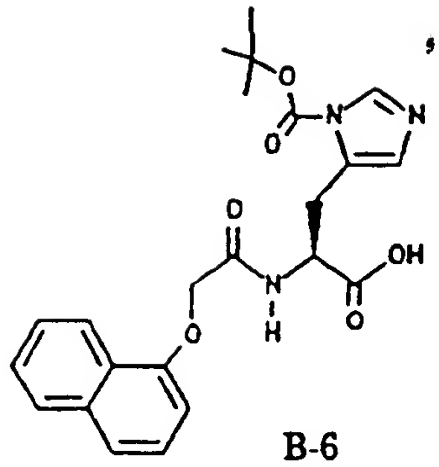


B-4

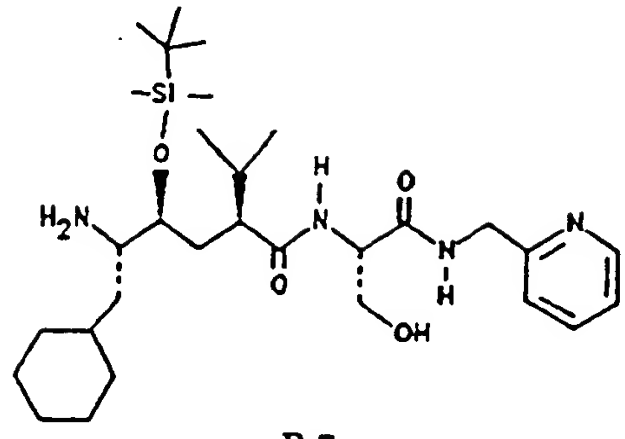


B-5

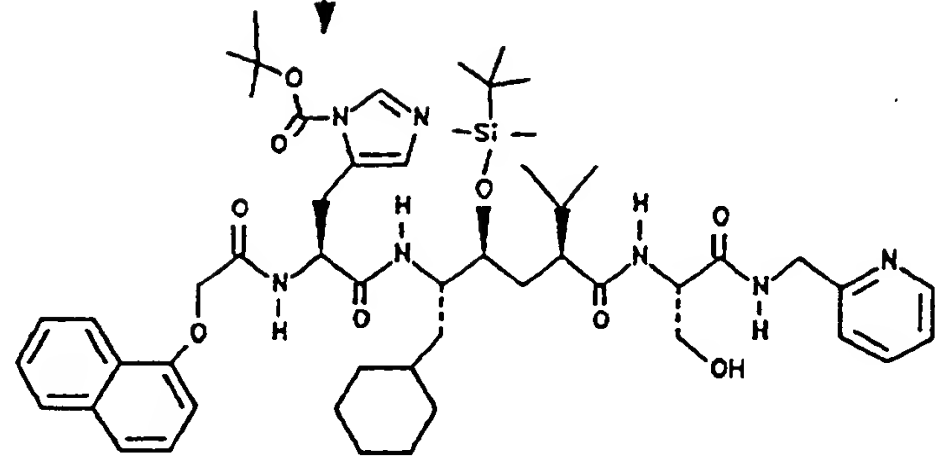
CHART B (continued)



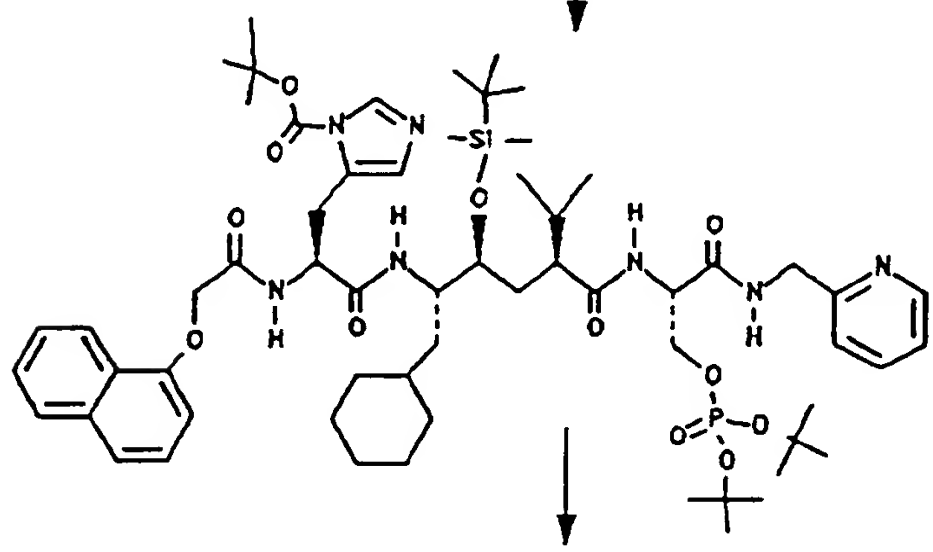
B-6



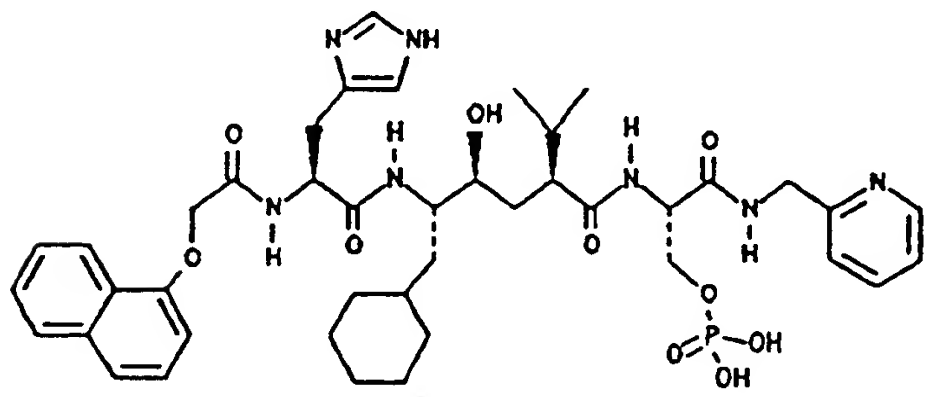
B-7



B-8



B-9



B-10

CHART C

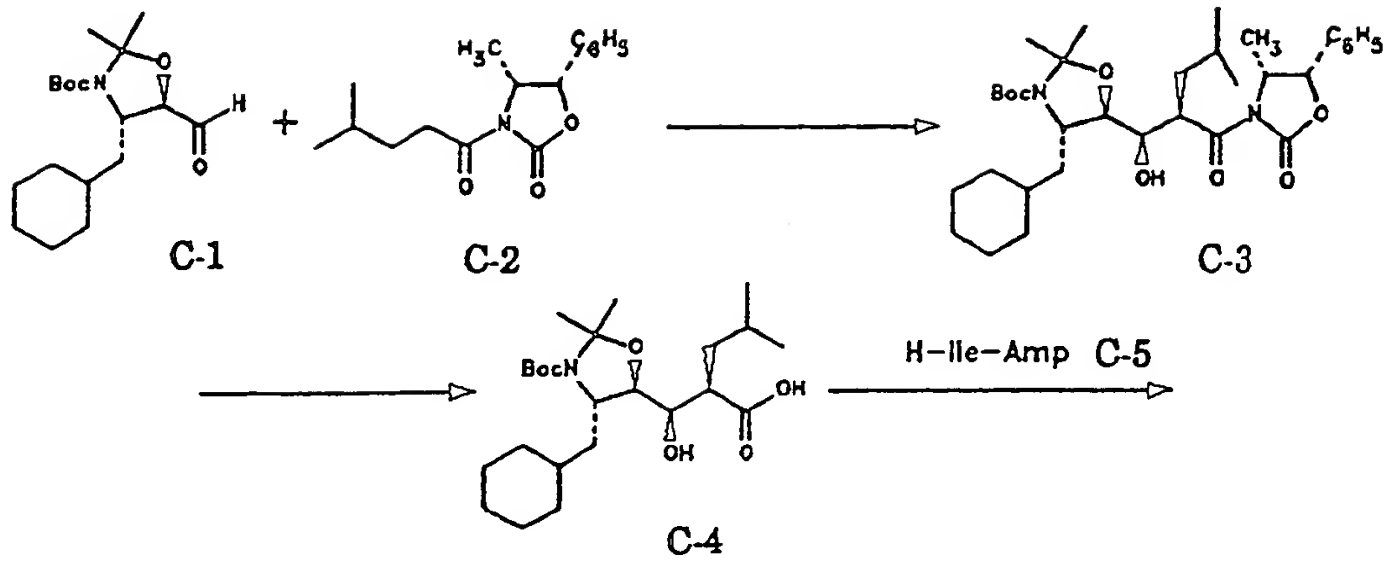
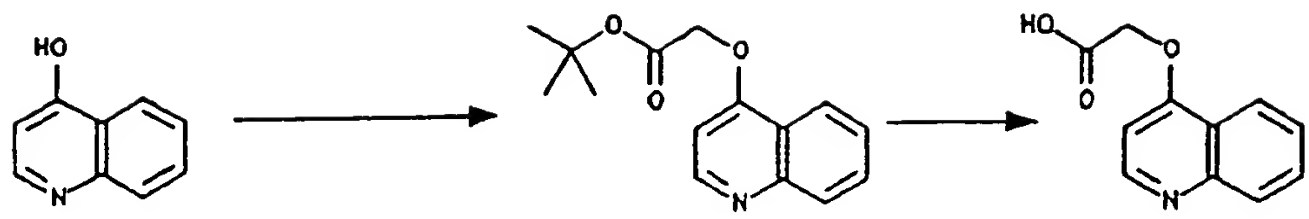
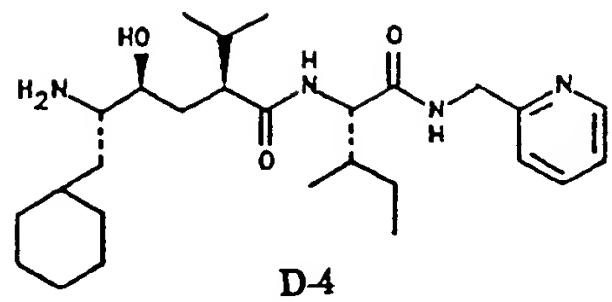

BocN
H
O
O
C-1
+
$H_3C$
$C_6H_5$
N
O
O
O
C-2
BocN
OH
O
O
$CH_3$
$C_6H_5$
C-3
BocN
OH
OH
O
C-4
H-Ile-Amp C-5
BocN
OH
O
O
C-6
$H_2N$
HO
OH
O
H
N
N
O
N
H
N
C-7
HO
H
N
O
OH
O
H
N
N
O
N
H
N
C-8

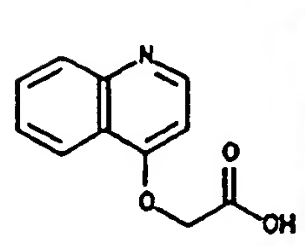
CHART D



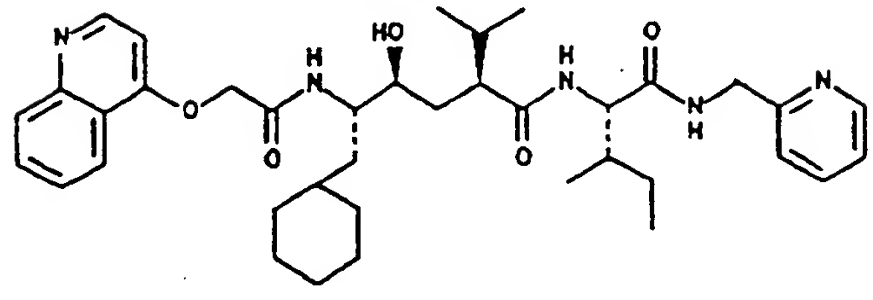
D-1 D-2 D-3



D-4

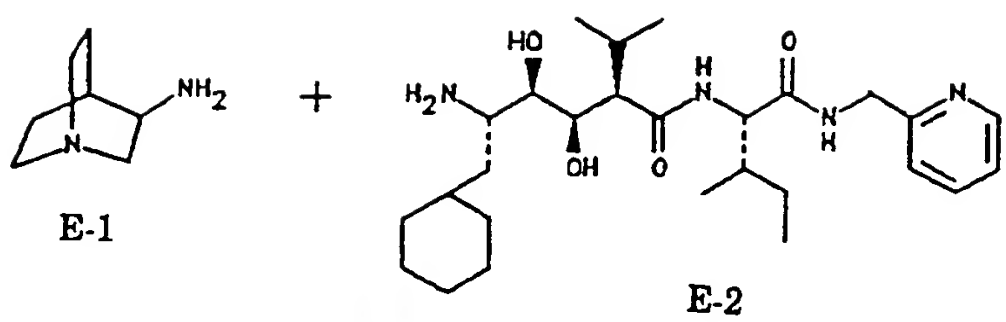


D-3



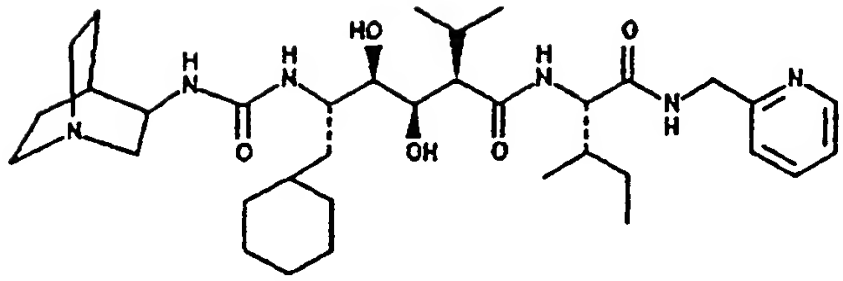
D-5

CHART E



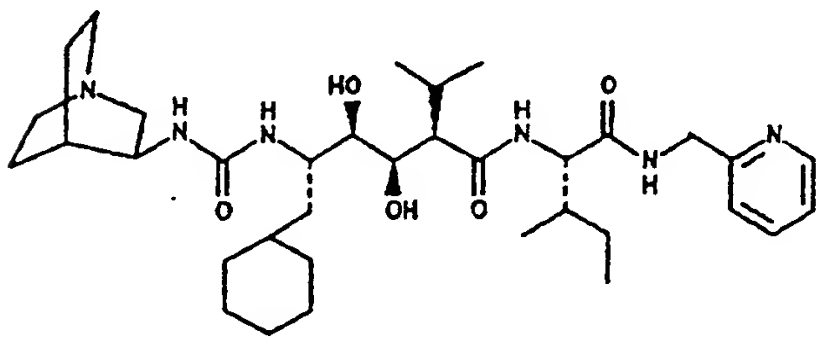
E-1

E-2



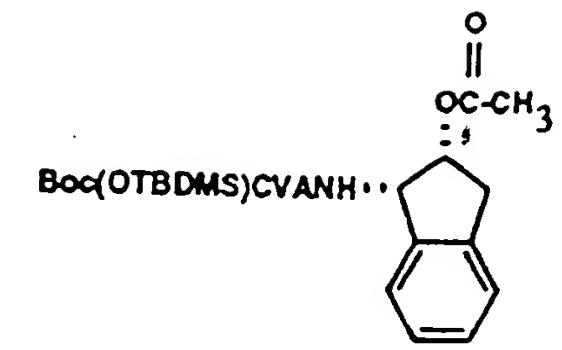
E-3

+

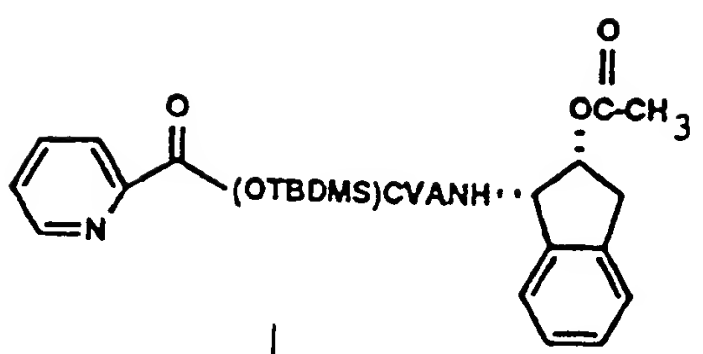


E-4

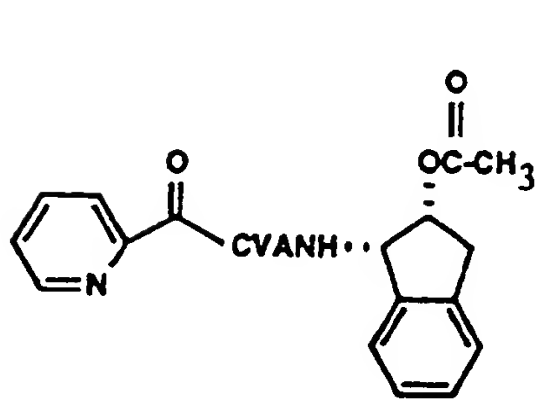
CHART F



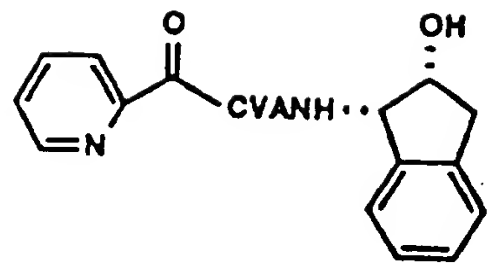

F-1




F-2

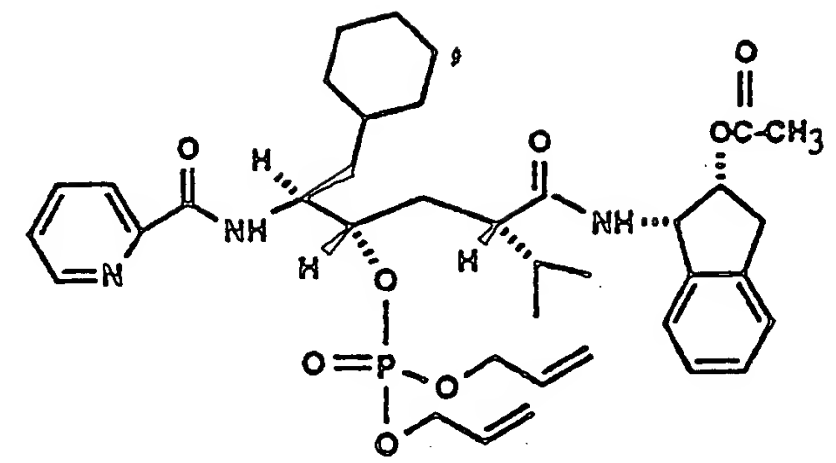



F-3

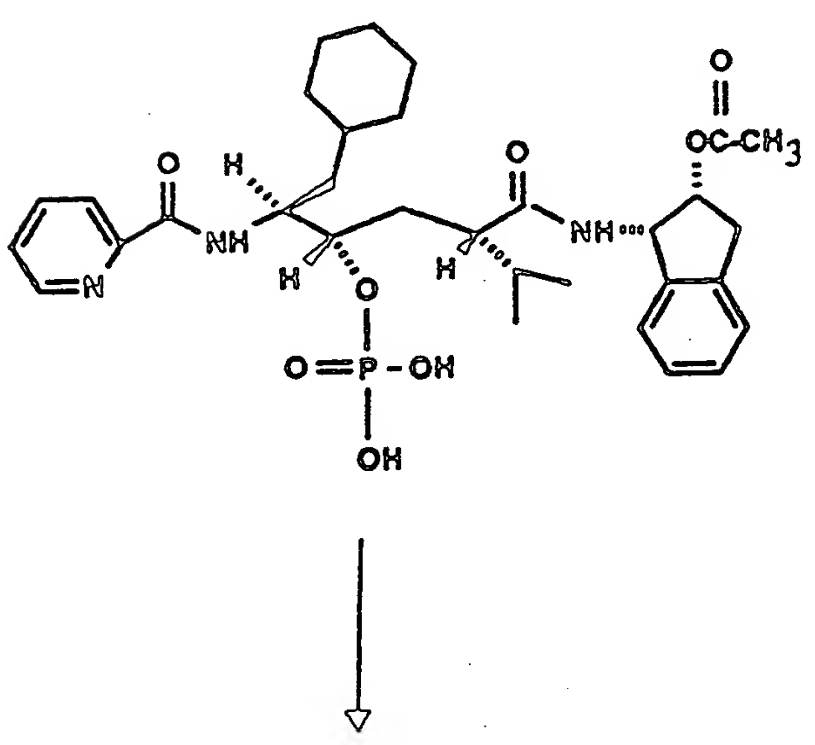



F-4

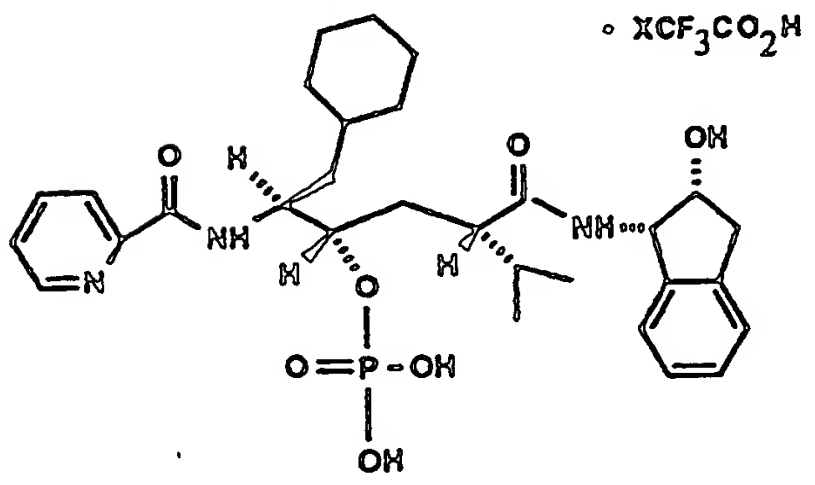
CHART F (continued)



F-5



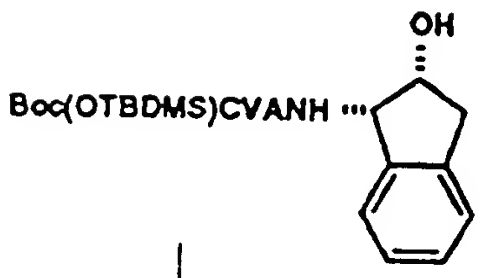
F-6



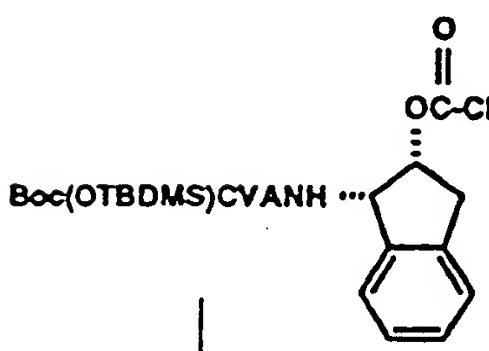
F-7

CHART G

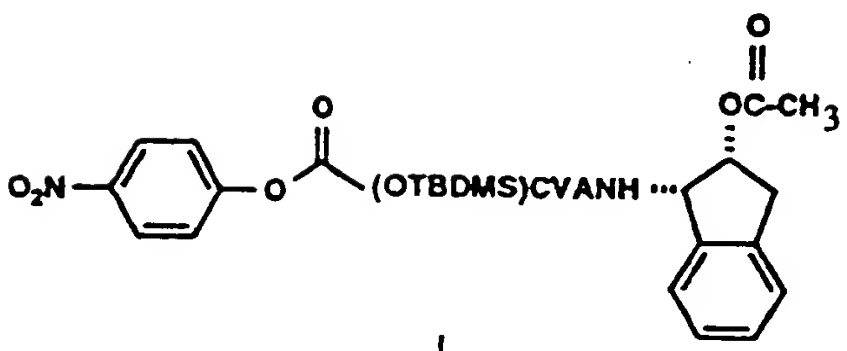
Boc(OTBDMS)CVAOH G-1




G-2

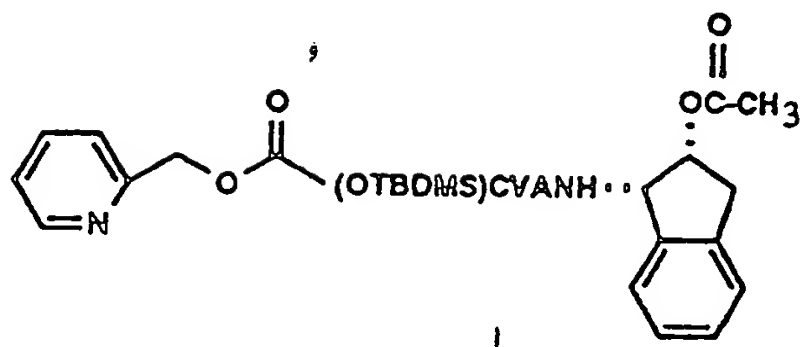



G-3

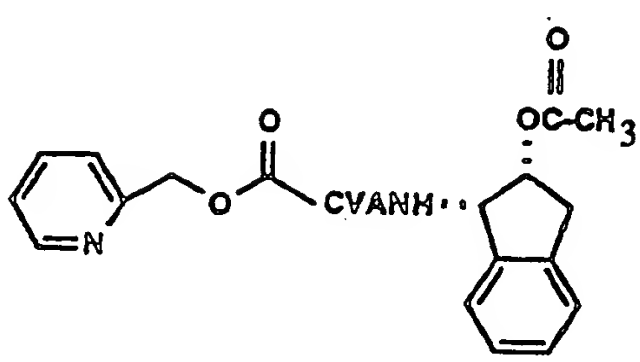



G-4

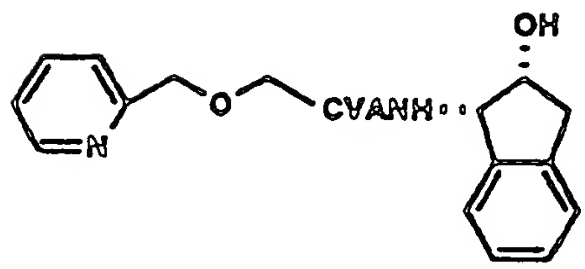
CHART G (continued)




G-5

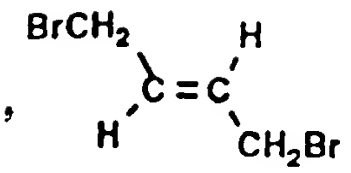



G-6

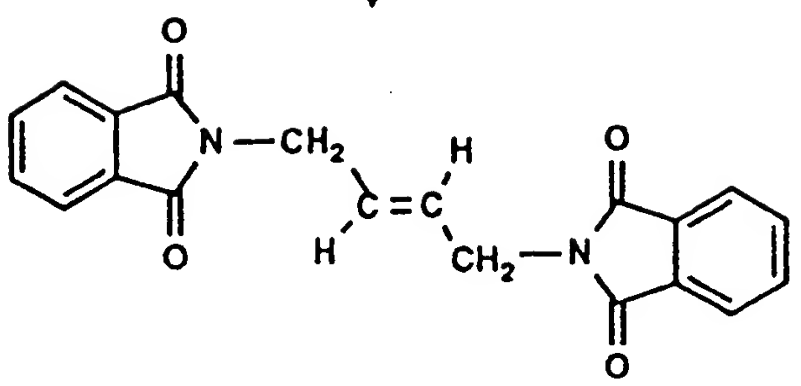



G-7

CHART H

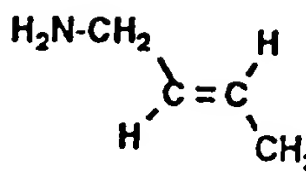


H-1

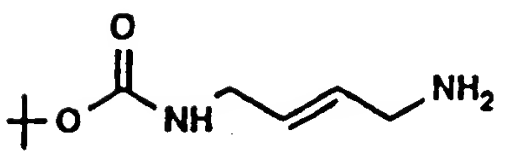


H-2

• 2HCl

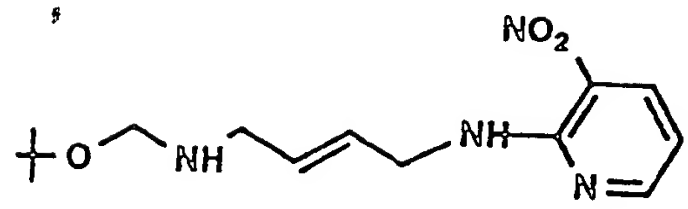


H-3

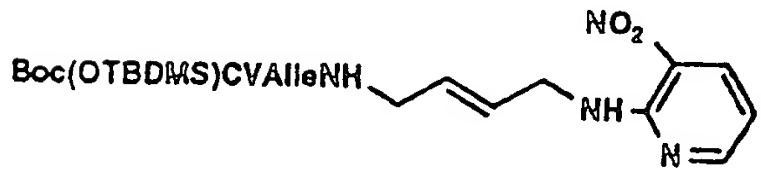


H-4

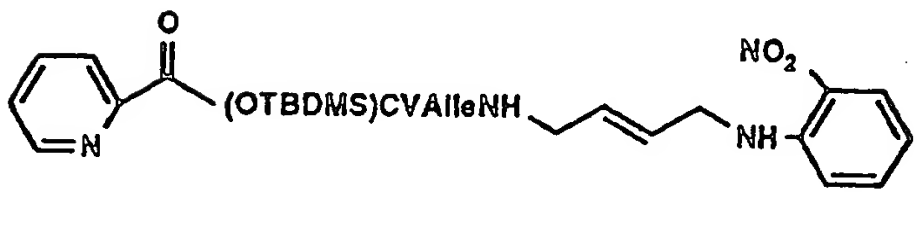
CHART H (continued)



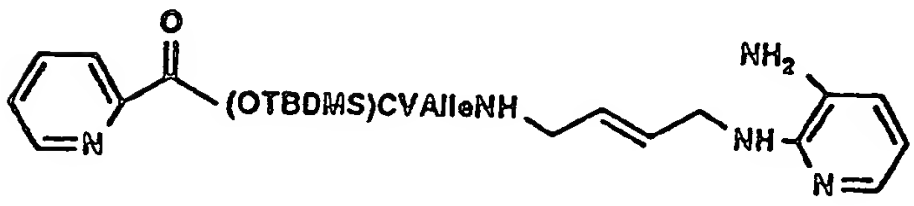
H-5



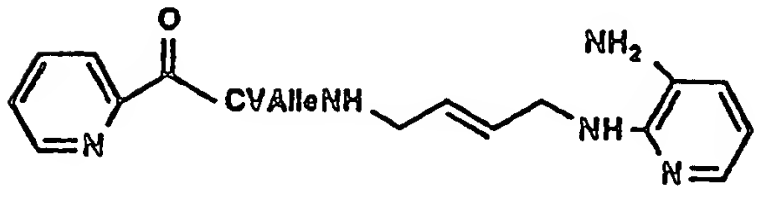
H-6



H-7

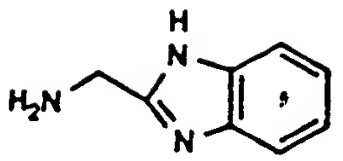


H-8



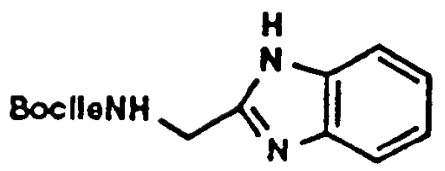
H-9

CHART I

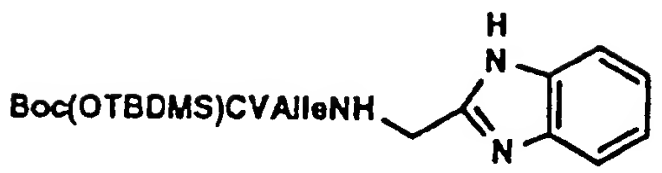


· 2HCl

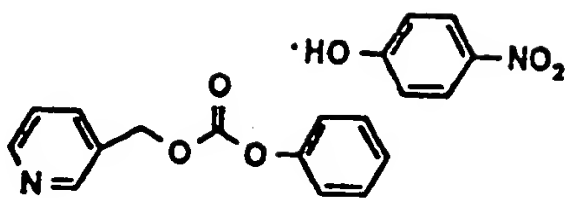
I-1



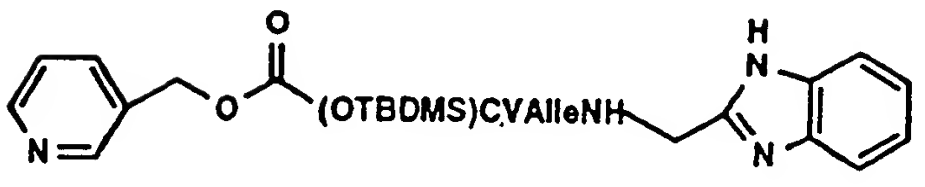
I-2



I-3

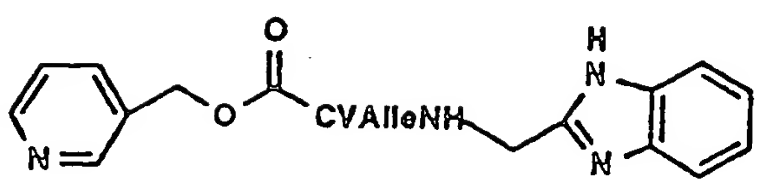


I-4

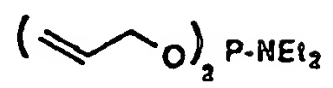


I-5

CHART I (continued)




I-6




I-7




I-8




I-9

CHART J

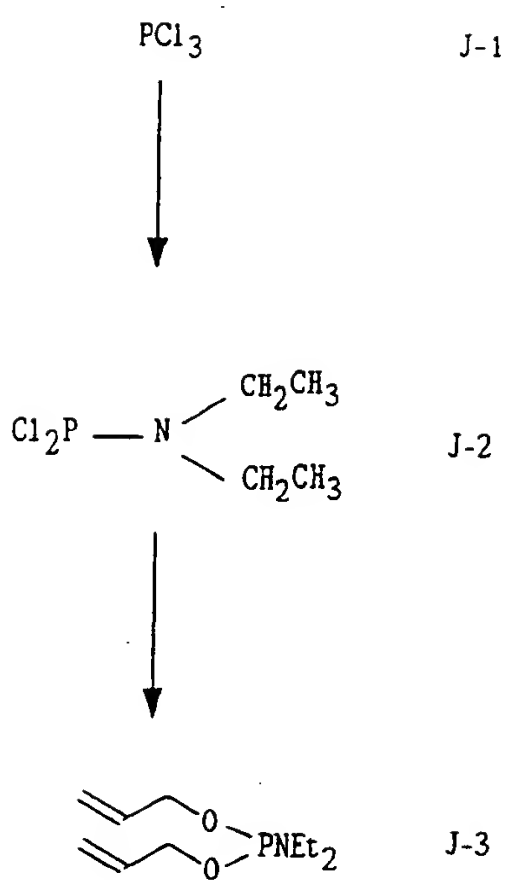


CHART K

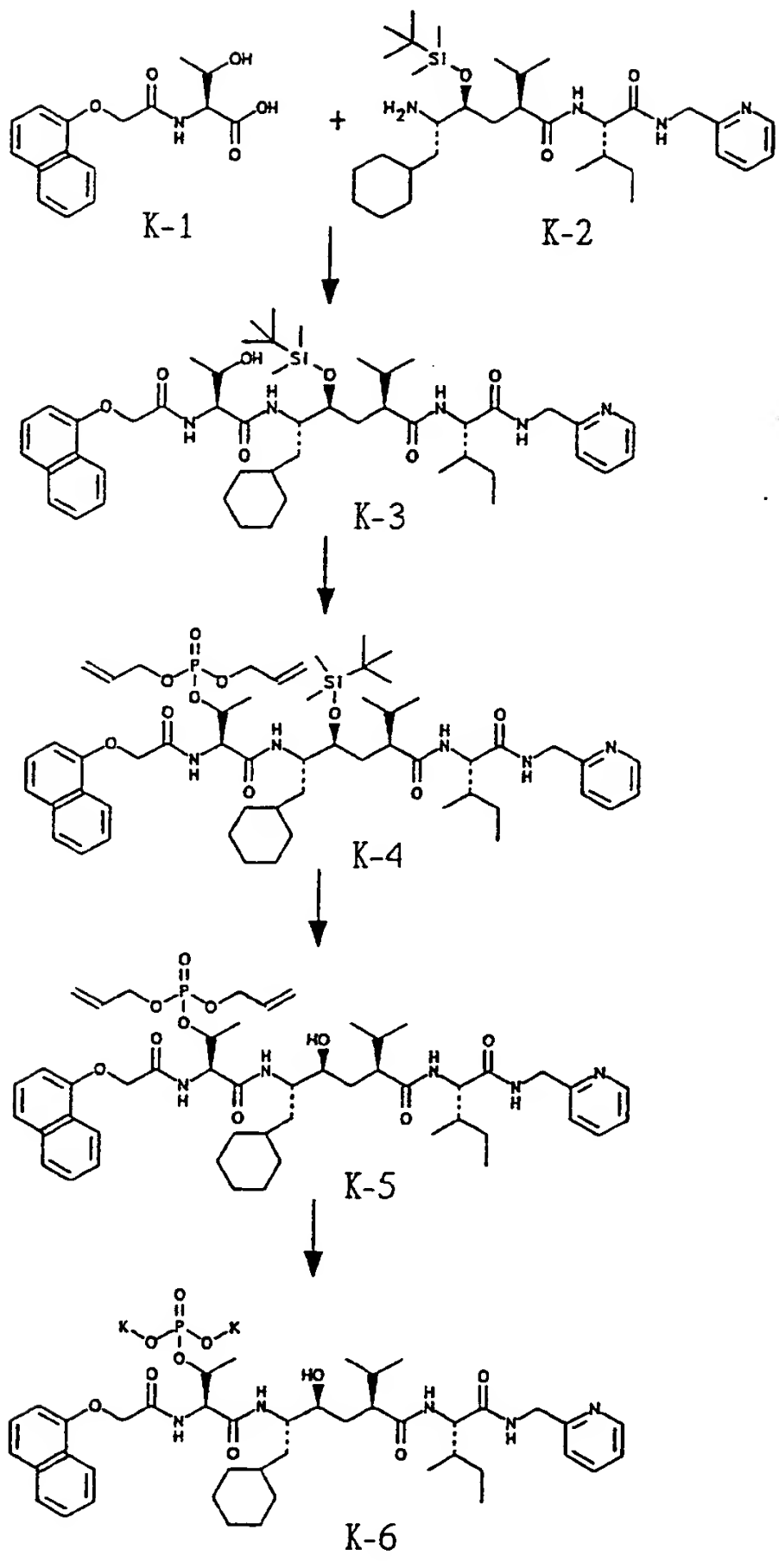


CHART L

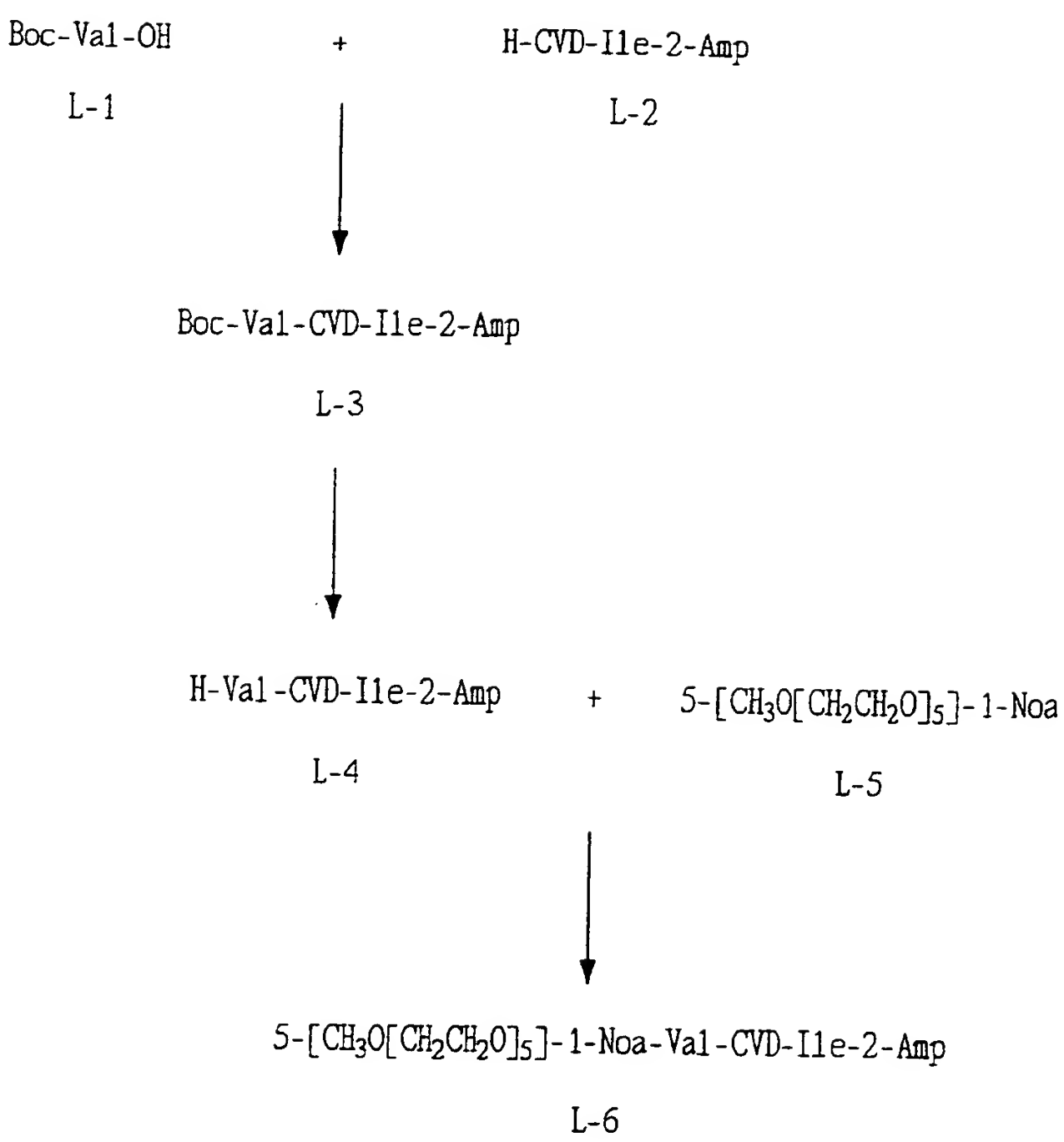
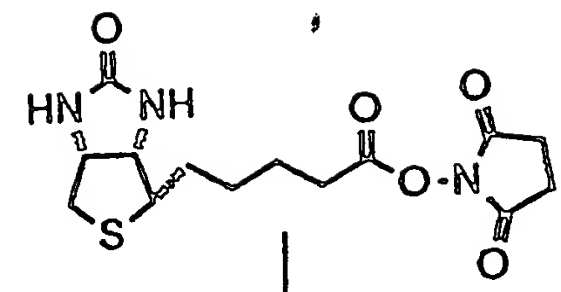
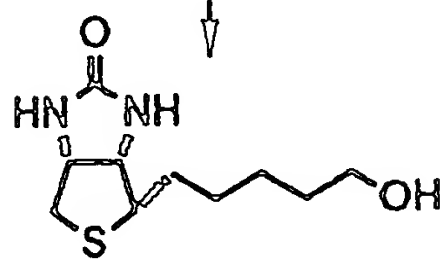

Boc-Val-OH
+
H-CVD-Ile-2-Amp
L-1
L-2
Boc-Val-CVD-Ile-2-Amp
L-3
H-Val-CVD-Ile-2-Amp
+
5-[CH3O[CH2CH2O]5]-1-Noa
L-4
L-5
5-[CH3O[CH2CH2O]5]-1-Noa-Val-CVD-Ile-2-Amp
L-6

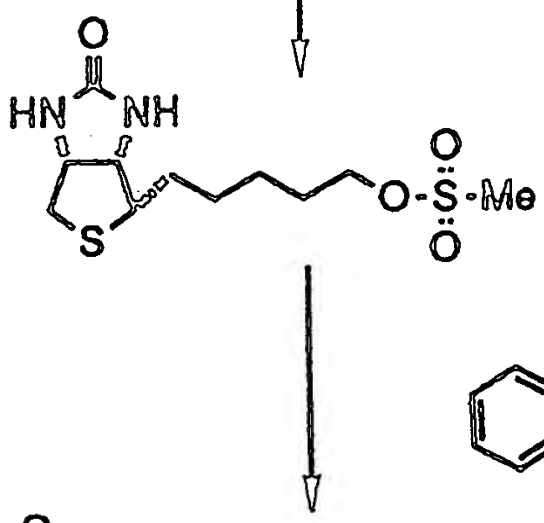
CHART M



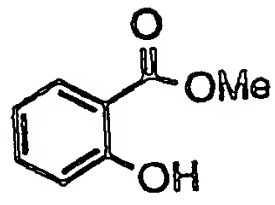
M-1



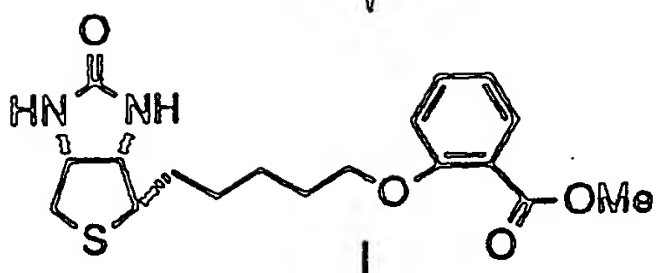
M-2



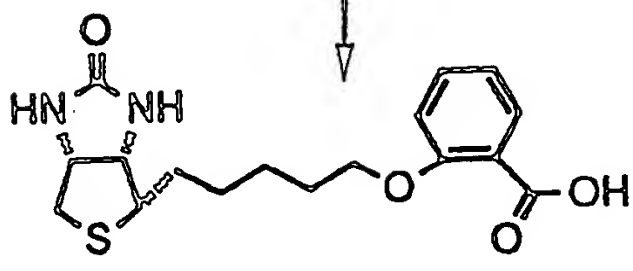
M-3



M-4

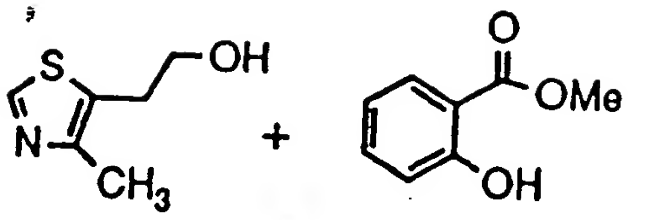


M-5

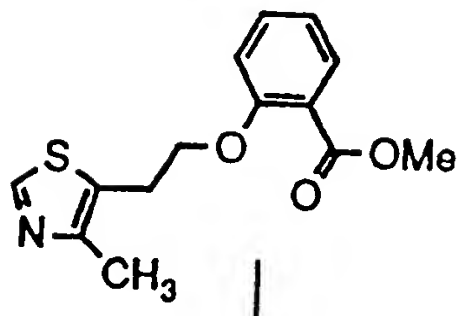


M-6

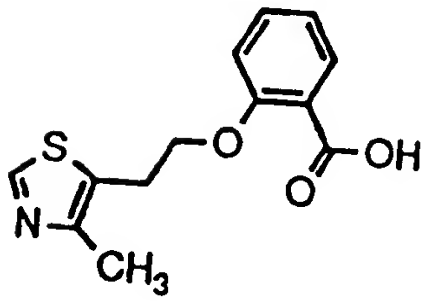
CHART N



N-1 N-2



N-3



N-4

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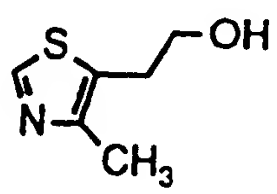


N-5

CHART N (continued)

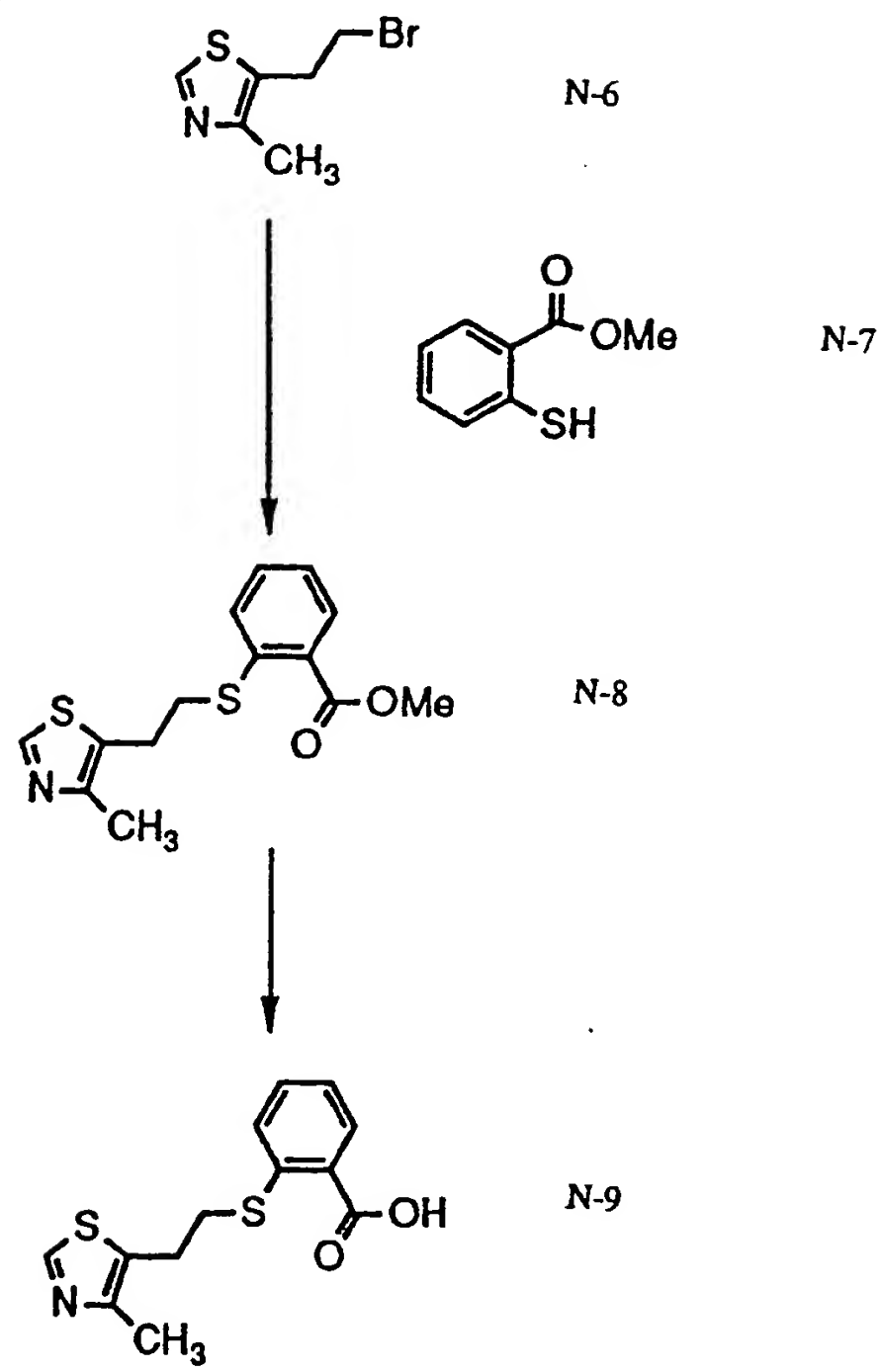


CHART O

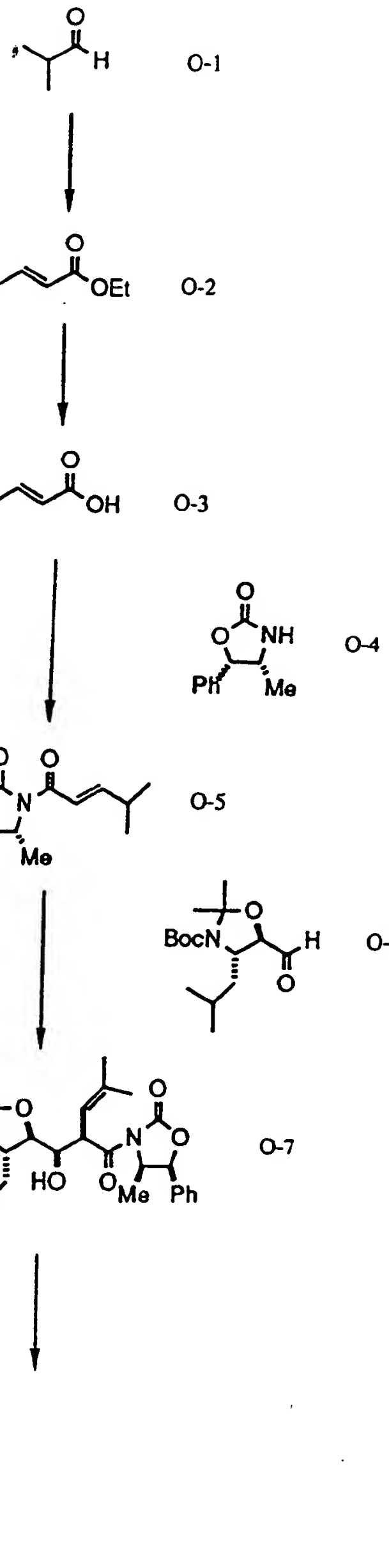
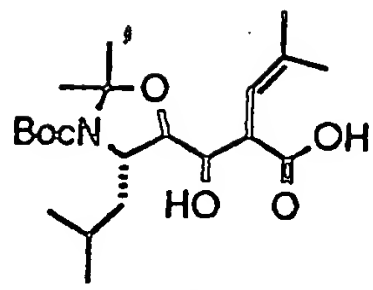
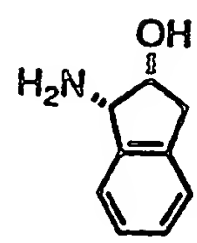

O
H
O-1
O
OEt
O-2
O
OH
O-3
O
O
NH
Ph
Me
O-4
O
O
N
Ph
Me
O-5
O
BocN
H
O
O-6
O
BocN
HO
O
N
O
Me
Ph
O-7

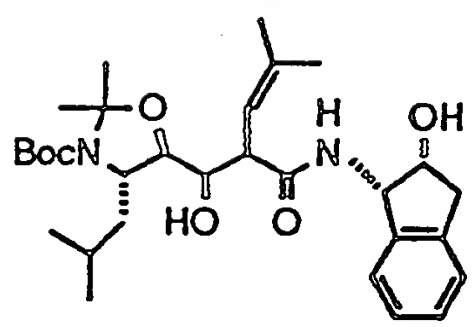
CHART O (continued)



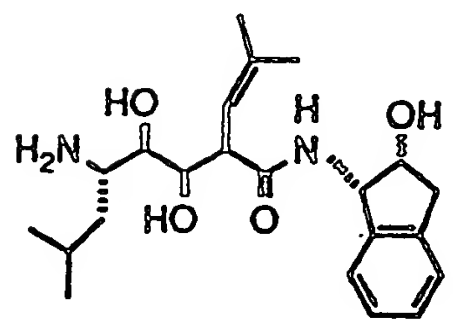
O-8



O-9



O-10



O-11

CLAIMS

1. A compound of the formula I

$$X_1\text{-}C_8\text{-}D_9\text{-}E_{10}\text{-}F_{11}\text{-}G_{12}\text{-}Z \qquad \text{I}$$

wherein $X_1$ is

a) hydrogen,

b) $C_1$-$C_7$ alkyl,

c) -$(CH_2)_p$-aryl,

d) -$(CH_2)_p$-Het,

e) -$(CH_2)_p$-$C_3$-$C_7$cycloalkyl,

f) $R_5$-O-$(CH_2)_q$-C(O)-,

g) $R_5$-$CH_2$-O-C(O)-,

h) $R_5$-O-C(O)-,

i) $R_5$-$(CH_2)_n$-C(O)-,

j) $R_5$-$(CH_2)_n$-C(S)-,

k) $R_4N(R_4)$-$(CH_2)_n$-C(O)-,

l) $R_5$-$SO_2$-$(CH_2)_q$-C(O)-,

m) $R_5$-$SO_2$-$(CH_2)_q$-O-C(O)-,

n) $R_5$-$(CH_2)_n$-$SO_2$,

o) Z-C(O)-CH(OH)-CH($CH_2R_1$)-C(O)-

p) $R_5$-$(CH_2)_p$ CH=CH-$(CH_2)_p$-C(O)-,

q) $R_5(CH_2)p$ CH=CH-$(CH_2)_p$-O-C(O),

r) $R_{27}(CH_2)_q$-C(O)-,

s) $(OH)_2(O)PO$-aryl-$(CH_2)_p$-C(O)-,

t) $(OH)_2(O)PO$-Het-$(CH_2)_p$-C(O)-,

u) aryl-$(W_1)_j$-$(CH_2)_m$-$W_1$-aryl-C(O)-,

v) aryl-$W_1$-$(CH_2)_m$-$W_1$-$(CH_2)_m$-C(O)-,

w) Het-$(CH_2)_m$-$W_1$-aryl-C(O)-,

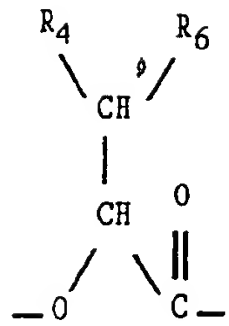
x) $C_1$-$C_6$ alkyl-CH(OH)-C(O)-,

y) biotinoyl,

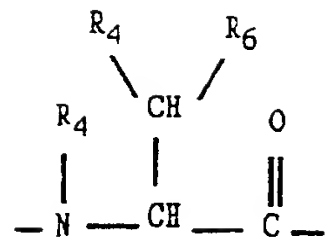
z) biotinoyl-NH-$(CH_2)_q$-C(O)-, or

a1) 2-((4-([3aS-(3aα,4β-6aα)]-1H-thieno-[3,4-d]imidazole-2(3H)-on-4yl)-pent-1-yl)-$W_1$-aryl-C(O)-;

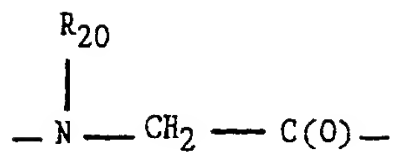
wherein $C_8$ is absent or a divalent moiety of the formula $XL_1$, $XL_2$, $XL_{2a}$, $XL_{2b}$ or other amino acyl derivative;



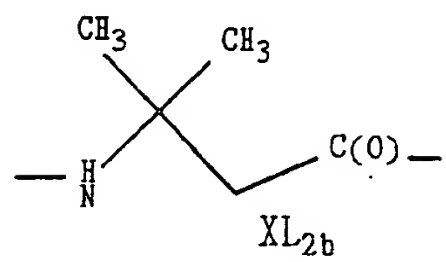
$XL_1$



$XL_2$

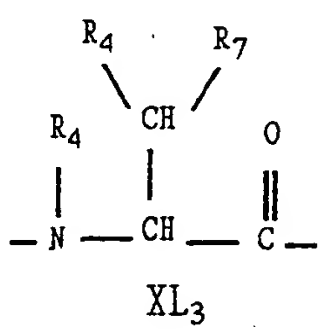


$XL_{2a}$

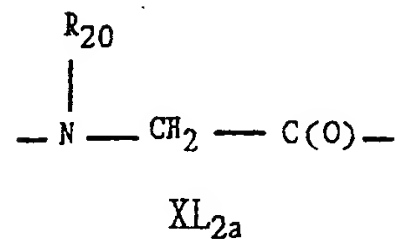


$XL_{2b}$

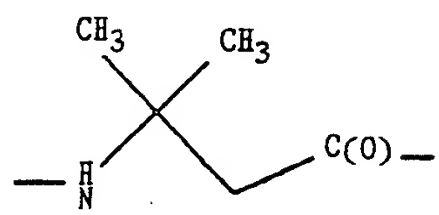
wherein $D_9$ is Pro, absent or a divalent moiety of the formula $XL_3$, $XL_{2a}$, $XL_{2b}$ or other amino acyl derivative;



$XL_3$

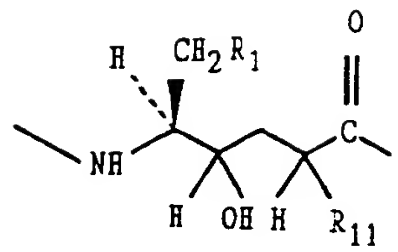


$XL_{2a}$

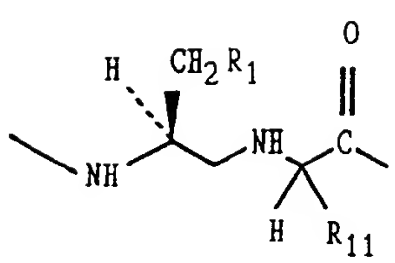


$XL_{2b}$

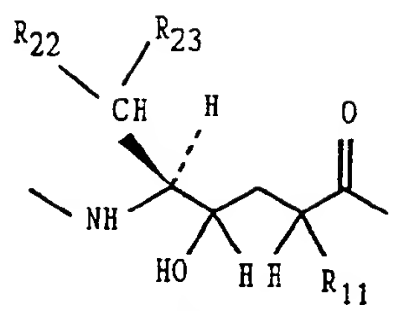
wherein $E_{10}$-$F_{11}$ is a divalent moiety of the formula $XL_6$, $XL_{6b}$, $XL_{6c}$, $XL_{6d}$, $XL_{6e}$, II, III, IV, $XL_{6p}$, $XL_{6cp}$, $XL_{6ep}$, $XL_{6ccp}$, $II_{cp}$, V, Vp, VI or VII;



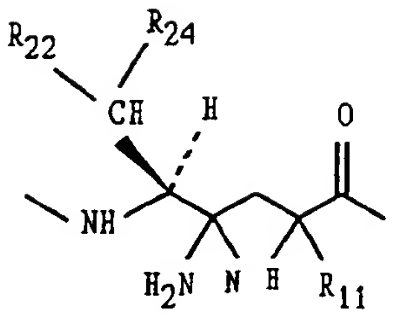
$XL_6$



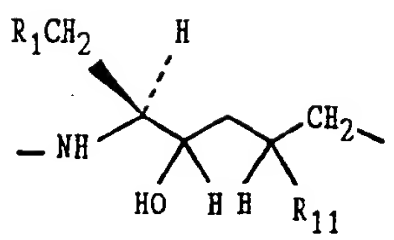
$XL_{6b}$



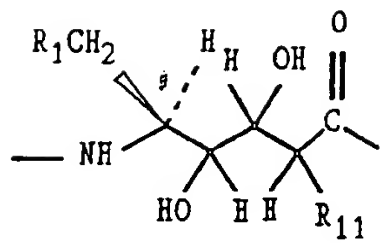
$XL_{6c}$



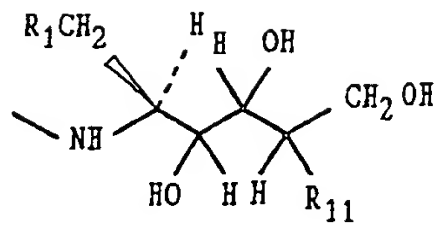
$XL_{6d}$



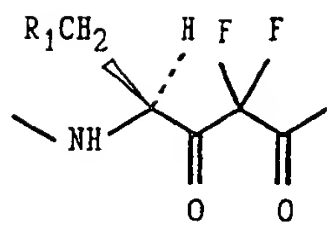
$XL_{6e}$



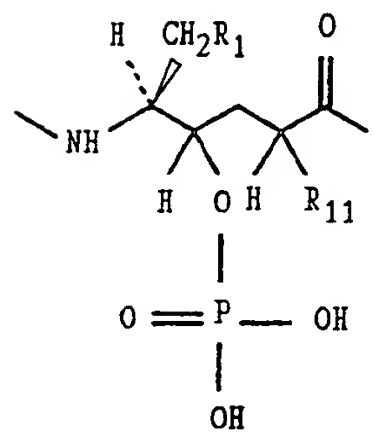
II



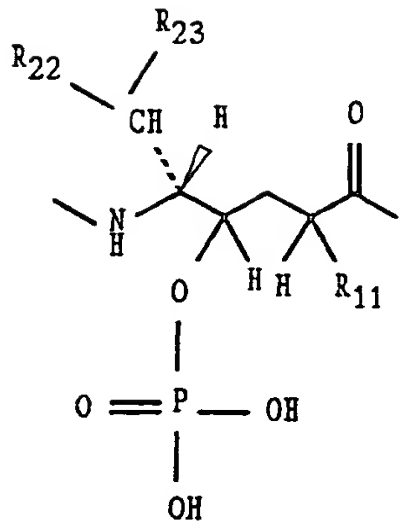
III



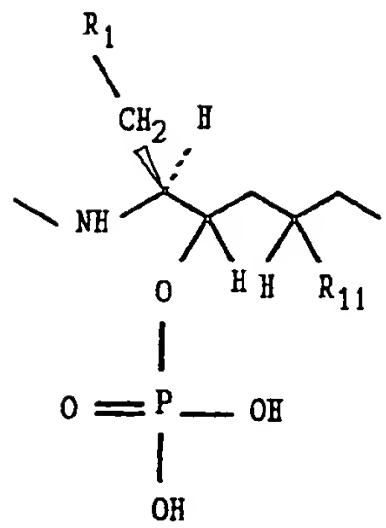
IV



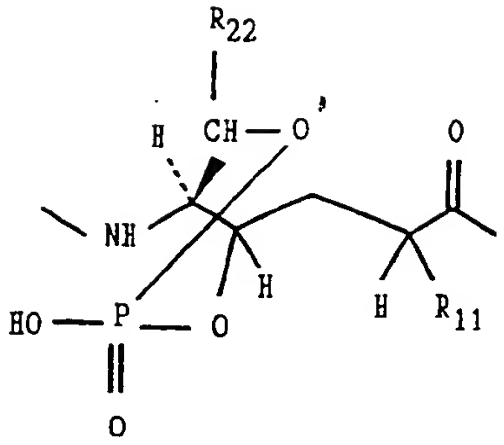
XL$_{6p}$



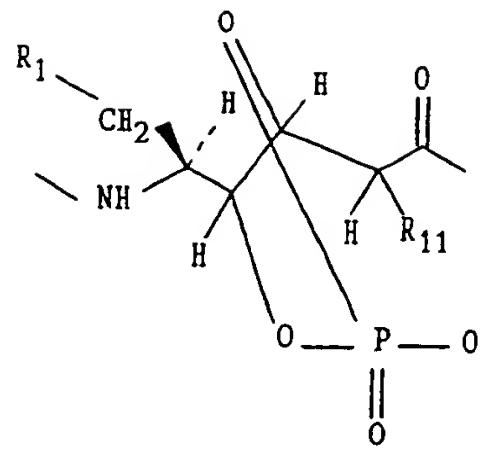
XL$_{6cp}$



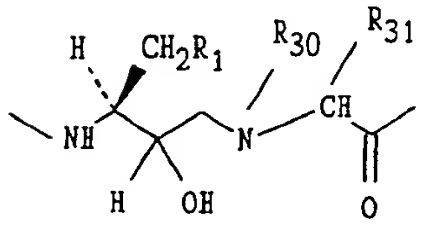
XL$_{6ep}$



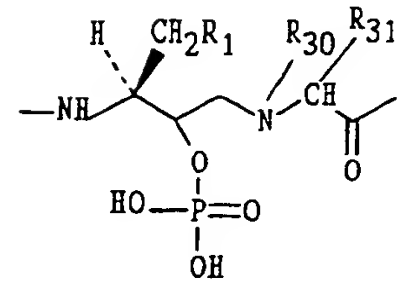
$XL_{6ccp}$



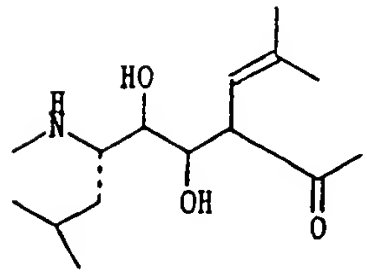
$II_{cp}$



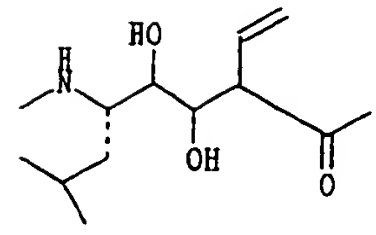
V



Vp

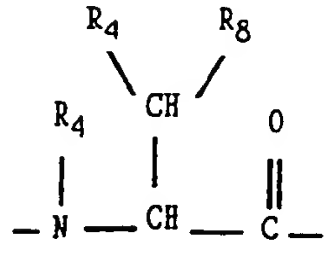


VI

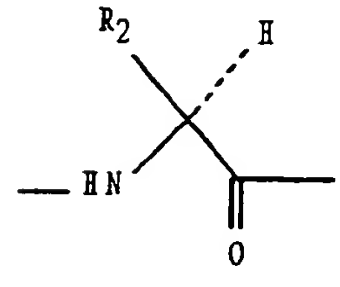


VII

wherein $G_{12}$ is absent or a divalent moiety of the formula $XL_4$, $XL_{4a}$ or other amino acyl derivative;



$XL_4$



$XL_{4a}$

wherein Z is

a) $-O-R_{10}$, ,

b) $-N(R_4)R_{14}$,

c) $C_4$-$C_8$cyclic amino,

d) $-NHR_{120}$,

e) $-NH-(CH_2)_r$ pyridine (N-oxide),

f) Het bonded via a nitrogen atom,

g) $-NH(CH_2)_qNH$-Het,

h) 1-amino indanyl optionally substituted at the 2- or 3- position by one or two hydroxy or $-OC(O)CH_3$,

i) 1-amino-2,3-cyclicmonophosphate indanyl, or

j) $-NH-(CH_2)_q-CH=CH-(CH_2)_q-NH$-Het;

wherein R is

a) $-(CH_2)_n$-isopropyl,

b) $-(CH_2)_n$-isobutyl,

c) $-(CH_2)_n$-phenyl, or

d) $-(CH_2)_n-C_3-C_7$cycloalkyl;

wherein $R_1$ is

a) hydrogen,

b) $C_1$-$C_5$alkyl,

c) aryl,

d) $C_3$-$C_7$cycloalkyl,

e) -Het,

f) $C_1$-$C_3$alkoxy, or

g) $C_1$-$C_3$alkylthio;

wherein $R_2$ is

a) hydrogen, or

b) $-CH(R_3)R_4$;

wherein $R_3$ is

a) hydrogen,

b) hydroxy,

c) $C_1$-$C_5$alkyl,

d) $C_3$-$C_7$cycloalkyl,

e) aryl,

f) -Het,

g) $C_1$-$C_3$alkoxy,

h) $C_1$-$C_3$alkylthio, or

i) -$OP(O)(OH)_2$;

wherein $R_4$ at each occurrence is the same or different as is

a) hydrogen,

b) $C_1$-$C_5$alkyl,

c) -$(CH_2)_p$-aryl,

d) -$(CH_2)_p$-Het,

e) -$(CH_2)_p$-$C_3$-$C_7$cycloalkyl, or

f) 1- or 2-adamantyl;

wherein $R_5$ is

a) $C_1$-$C_6$alkyl,

b) $C_3$-$C_7$cycloalkyl,

c) aryl,

d) -Het,

e) 5-oxo-2-pyrrolidinyl,

f) 1 or 2-adamantyl,

g) -aryl-$OP(O)(OH)_2$, or

h) -Het-$OP(O)(OH)_2$;

wherein $R_6$ is

a) hydrogen,

b) $C_1$-$C_5$alkyl,

c) -$(CH_2)_p$-aryl,

d) -$(CH_2)_p$-Het,

e) -$(CH_2)_p$-$C_3$-$C_7$cycloalkyl,

f) 1- or 2-adamantyl,

g) -$(CH_2)_p$-aryl-$OP(O)(OH)_2$,

h) -$(CH_2)_p$-Het-$OP(O)(OH)_2$, or

i) -$(CH_2)_p$-$OP(O)(OH)_2$;

wherein $R_7$ is

a) hydrogen,

b) $C_1$-$C_5$alkyl,

c) -$(CH_2)_n$-hydroxy,

d) amino $C_1$-$C_4$alkyl-,

e) guanidinyl $C_1$-$C_3$alkyl-,

f) aryl,

g) -Het,

h) methylthio,

i) $-(CH_2)_p-C_3-C_7$cycloalkyl,

j) amino,

k) $-(CH_2)_n-COOH$,

l) $-(CH_2)_n-COOC_1-C_6$ alkyl,

m) $-(CH_2)_n-CONR_{22}R_{26}$,

n) $-(CH_2)_n-OP(O)(OH)_2$,

o) -aryl-$OP(O)(OH)_2$, or

p) -Het-$OP(O)(OH)_2$;

wherein $R_8$ is

a) hydrogen

b) $C_1-C_5$alkyl,

c) hydroxy,

d) aryl,

e) -Het,

f) guanidinyl $C_1-C_3$alkyl-,

g) $-(CH_2)_p-C_3-C_7$cycloalkyl, or

h) $-OP(O)(OH)_2$;

wherein $R_{10}$ is

a) hydrogen,

b) $C_1-C_5$alkyl,

c) $-(CH_2)_nR_{16}$,

d) $-(CH_2)_nR_{17}$,

e) $C_3-C_7$cycloalkyl,

f) a pharmaceutically acceptable cation,

g) $-CH(_{25})-CH_2-R_{15}$, or

h) $-CH_2-CH(R_{12})-R_{15}$;

wherein $R_{11}$ is -R or $-R_2$;

wherein $R_{12}$ is $-(CH_2)_n-R_{13}$;

wherein $R_{13}$ is

a) aryl,

b) amino,

c) mono-, di- or tri-$C_1-C_3$alkylamino,

d) -Het,

e) $C_1-C_5$alkyl,

f) $C_3-C_7$cycloalkyl,

g) $C_2$-$C_5$alkenyl,

h) $C_3$-$C_7$cycloalkenyl,

i) hydroxy, ,

j) $C_1$-$C_3$alkoxy,

k) $C_1$-$C_3$alkanoyloxy,

l) mercapto,

m) $C_1$-$C_3$alkylthio,

n) -COOH,

o) -CO-O-$C_1$-$C_6$alkyl,

p) -CO-O-$CH_2$-($C_1$-$C_3$alkyl)-N($C_1$-$C_3$alkyl)$_2$,

q) -CO-N$R_{22}R_{26}$;

r) $C_4$-$C_7$cyclic amino,

s) $C_4$-$C_7$cycloalkylamino,

t) guanidyl,

u) cyano,

v) N-cyanoguanidyl,

w) cyanoamino,

x) (hydroxy $C_2$-$C_4$alkyl)amino, or

y) di-(hydroxy$C_2$-$C_4$alkyl)amino;

wherein $R_{14}$ is

a) hydrogen,

b) $C_1$-$C_{10}$alkyl,

c) -$(CH_2)_n$-$R_{18}$,

d) -$(CH_2)_n$-$R_{19}$,

e) -CH($R_{25}$)-$CH_2$-$R_{15}$,

f) -$(CH_2)_q$-CH($R_{12}$)-$R_{15}$,

g) (hydroxy $C_1$-$C_8$alkyl),

h) hydroxy $C_1$-$C_8$ alkyl-aryl, or

i) ($C_1$-$C_3$ alkoxy) $C_1C_8$ alkyl;

wherein $R_{15}$ is

a) hydroxy,

b) $C_3$-$C_7$cycloalkyl,

c) aryl,

d) amino,

e) mono-, di-, or tri-$C_1$-$C_3$alkylamino,

f) mono- or di-(hydroxy $C_2$-$C_4$alkyl)amino,

g) -Het,

h) $C_1$-$C_3$alkoxy-,

i) $C_1$-$C_3$alkanoyloxy-,

j) mercapto,

k) $C_1$-$C_3$alkylthio-,

l) $C_1$-$C_5$alkyl,

m) $C_4$-$C_7$cyclic amino,

n) $C_4$-$C_7$cycloalkylamino,

o) $C_1$-$C_5$alkenyloxy, or

p) $C_3$-$C_7$cycloalkenyl;

wherein $R_{16}$ is

a) aryl,

b) amino,

c) mono- or di-($C_1$-$C_3$alkyl)amino,

d) hydroxy,

e) $C_3$-$C_7$cycloalkyl,

f) $C_4$-$C_7$cyclic amino, or

g) $C_1$-$C_3$alkanoyloxy;

wherein $R_{17}$ is

a) -Het,

b) $C_1$-$C_5$alkenyl,

c) $C_3$-$C_7$cycloalkenyl,

d) $C_1$-$C_3$alkoxy,

e) mercapto,

f) $C_1$-$C_3$alkylthio,

g) -COOH,

h) -CO-O-$C_1$-$C_6$alkyl,

i) -CO-O-$CH_2$-($C_1$-$C_3$alkyl)-N($C_1$-$C_3$alkyl)$_2$,

j) -CO-N$R_{22}R_{26}$,

k) tri-$C_1$-$C_3$alkylamino,

l) guanidyl,

m) cyano,

n) N-cyanoguanidyl,

o) (hydroxy $C_2$-$C_4$alkyl)amino,

p) di-(hydroxy $C_2$-$C_4$alkyl)amino, or

q) cyanoamino;

wherein $R_{18}$ is

a) amino,

b) mono-, or di-($C_1$-$C_3$alkyl)amino,

c) $C_4$-$C_7$cyclic amino,

d) $C_4$-$C_7$cycloalkylamino, or

e) -$CH(NH_2)(CO_2H)$;

wherein $R_{19}$ is

a) aryl,

b) -Het,

c) tri-$C_1$-$C_3$alkylamino,

d) $C_3$-$C_7$cycloalkyl,

e) $C_2$-$C_5$alkenyl,

f) $C_3$-$C_7$cycloalkenyl,

g) hydroxy,

h) $C_1$-$C_3$alkoxy,

i) $C_1$-$C_3$alkanoyloxy,

j) mercapto,

k) $C_1$-$C_3$alkylthio,

l) -COOH,

m) -CO-O-$C_1$-$C_6$alkyl,

n) -CO-O-$CH_2$-($C_1$-$C_3$alkyl)-N($C_1$-$C_3$alkyl)$_2$,

o) -CO-$NR_{22}R_{26}$,

p) guanidyl,

q) cyano,

r) N-cyanoguanidyl,

s) cyanoamino,

t) (hydroxy $C_2$-$C_4$alkyl)amino,

u) di-(hydroxy $C_2$-$C_4$alkyl)amino, or

v) -$SO_3H$;

wherein $R_{20}$ is

a) hydrogen,

b) $C_1$-$C_5$alkyl, or

c) aryl-$C_1$-$C_5$alkyl;

wherein $R_{22}$ is

a) hydrogen, or

b) $C_1$-$C_3$alkyl;

wherein $R_{23}$ is

a) $-(CH_2)_n-OH$,

b) $-(CH_2)_n-NH_2$,

c) aryl,

d) $C_1$-$C_3$alkyl, or

e) $-(CH_2)_n-OP(O)(OH)_2$;

wherein $R_{24}$ is

a) $-R_1$,

b) $-(CH_2)_n-OH$,

c) $-(CH_2)_n-NH_2$, or

d) $-(CH_2)_n-OP(O)(OH)_2$;

wherein $R_{25}$ is

a) $-(CH_2)_n-R_{13}$,

b) hydrogen,

c) $C_1$-$C_3$alkyl, or

d) phenyl-$C_1$-$C_3$alkyl;

wherein $R_{26}$ is

a) hydrogen,

b) $C_1$-$C_3$alkyl, or

c) phenyl-$C_1$-$C_3$alkyl;

wherein $R_{27}$ is

a) -COOH,

b) $-COOC_1$-$C_6$ alkyl,

c) $-CONR_{22}R_{26}$,

d) $-CH(NH_2)COOH$, or

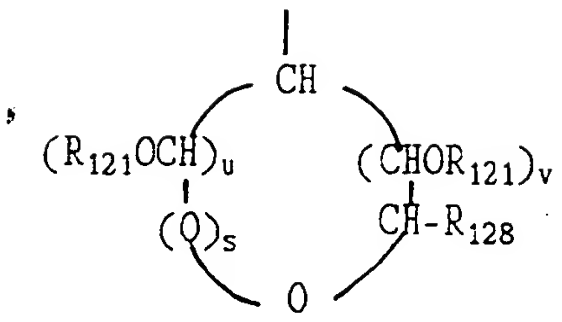
e) hydroxy;

wherein $R_{30}$ and $R_{31}$ together represent a trimethylene or tetramethylene group which is optionally substituted by hydroxy, alkoxycarbonylamino or acylamino or in which one $-CH_2-$ group is replaced by -NH-, -N(alkoxycarbonyl)-, -N(acyl)- or -S- or which carries a fused cycloalkane, aromatic or heteroaromatic ring;

wherein $R_{120}$ is

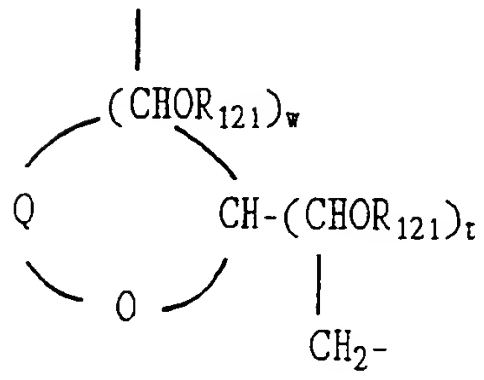
a) $R_{126}C[(CH_2)_qOR_{121}]_2(CH_2)_q-$,

b)



XXX

c)

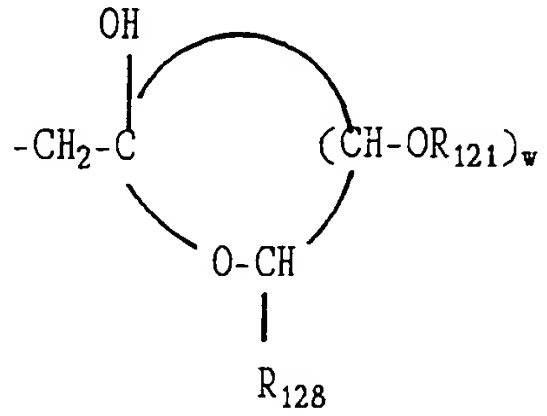


XXXI

d) $-CH_2(CHOR_{121})_xCH_2OR_{121}$,

e) $R_{121}OCH_2(CHOR_{121})_yCH\text{-}(CHOR_{121})_zCH_2OR_{121}$,

f)



XXXII ,or

g) $R_{121}OCH_2\text{-}C(CH_2OR_{121})_2\text{-}$;

wherein $R_{121}$ is

a) hydrogen,

b) $C_1$-$C_6$alkyl,

c) $-(CH_2)_n$-aryl, or

d) $-C(O)R_{123}$;

wherein $R_{123}$ is

a) $C_1$-$C_5$ alkyl, or

b) $-(CH_2)_n$-phenyl;

wherein $R_{126}$ is

a) hydrogen, or

b) $(CH_2)_nOR_{121}$;

wherein $R_{128}$ is

a) hydrogen, or

b) $-(CHOR_{121})_tCH_2OR_{121}$;

wherein Q is

a) $CH_2$,

b) $CHOR_{121}$, or

c) C(O);

wherein $W_1$ is

a) -O-, or

b) -S-;

wherein j is zero or one;

wherein m is one to three, inclusive;

wherein for each occurrence n is independently an integer of zero to six, inclusive;

wherein p is zero to two, inclusive;

wherein q is an integer of one to six, inclusive;

wherein r is zero to five, inclusive;

wherein s is an integer of zero or one so that the sum of u plus v plus s is three or four;

wherein t is an integer of zero to three, inclusive;

wherein u is an integer of zero to three, inclusive;

wherein v is an integer of zero to four, inclusive;

wherein w is an integer of two or three;

wherein x is an integer of two to seven, inclusive;

wherein y is an integer of zero to six, inclusive; and

wherein z is an integer of zero to six so that the sum of y plus z does not exceed six;

wherein aryl is phenyl or naphthyl substituted by zero to three of the following:

a) $C_1$-$C_3$alkyl,

b) hydroxy,

c) $C_1$-$C_3$alkoxy,

d) halo,

e) amino,

f) mono- or di-$C_1$-$C_3$alkylamino,

g) -CHO,

h) -COOH,

i) $COOR_{26}$,

j) $CONHR_{26}$,

k) nitro,

l) mercapto,

m) $C_1$-$C_3$alkylthio,

n) $C_1$-$C_3$alkylsulfinyl,

o) $C_1$-$C_3$alkylsulfonyl,

p) -N($R_4$)-$C_1$-$C_3$alkylsulfinyl,

q) -$SO_3H$,

r) $SO_2NH_2$,

s) -CN,

t) -$CH_2NH_2$,

u) -O[$(CH_2)_2O]_qCH_3$,

v) -[O-$(CH_2)_2]_q$-$OCH_3$,

w) -[O-$(CH_2)_2]_q$-$NR_{22}R_{26}$,

x) -[O-$(CH_2)_2]_q$-Het, or

y) -O-C(O)-$C_1$-$C_3$ alkyl;

wherein -Het is a 5- or 6-membered saturated or unsaturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another heterocycle and the ring may be connected through a carbon or secondary nitrogen in the ring or an exocyclic nitrogen; and if chemically feasible, the nitrogen and sulfur atoms may be in the oxidized forms; and substituted by zero to three of the following:

a) $C_1$-$C_5$alkyl,

b) hydroxy,

c) hydroxy ($C_1$-$C_5$alkyl),

d) halogen,

e) amino,

f) amino ($C_1$-$C_5$alkyl),

g) -CHO,

h) -$CO_2H$,

i) -$CO_2$-($C_1$-$C_5$alkyl),

j) -$CONH_2$,

k) -CONH-($C_1$-$C_5$alkyl),

l) nitro,

m) mercapto,

n) mercapto ($C_1$-$C_5$alkyl),

o) -$SO_3H$,

p) -$SO_2NH_2$,

q) -CN,

r) -O-$C_1$-$C_5$alkyl, or

s) -[O-($CH_2$)$_2$]$_q$-$OCH_3$;

and pharmacologically acceptable salts thereof;

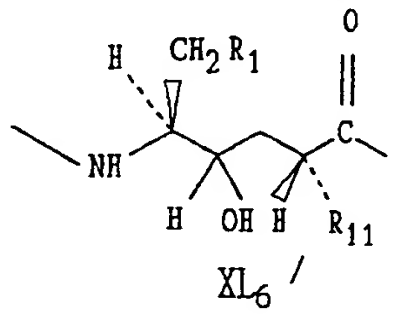
with the provisos that:

1) at least one phosphate group must be present; and

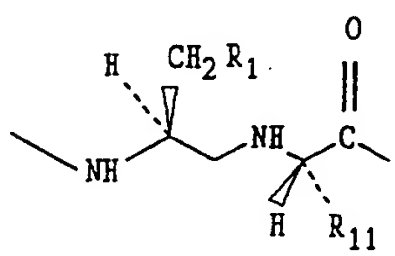
2) no more than three phosphate groups are present.

2. The compound of claim 1

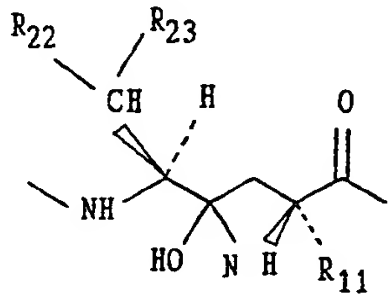
wherein $E_{10}$-$F_{11}$ is a divalent moiety of the formula $XL_6'$, $XL_{6b}'$, $XL_{6c}'$, $XL_{6d}'$, $XL_{6e}'$, II', III', IV, $XL_{6p}'$, $XL_{6cp}'$, $XL_{6ep}'$, $XL_{6ccp}'$, $II_{cp}'$, V or Vp;



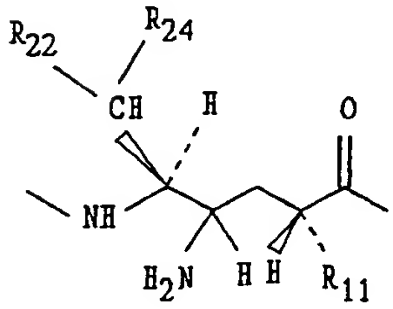
$XL_6$



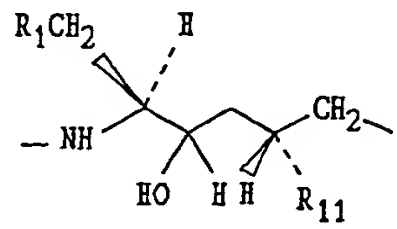
$XL_{6b}$



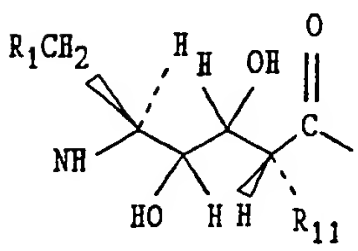
$XL_{6c}$



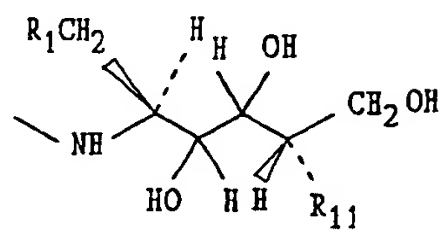
$XL_{6d}$



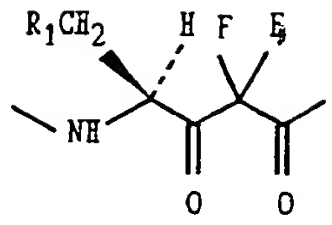
$XL_{6e}$



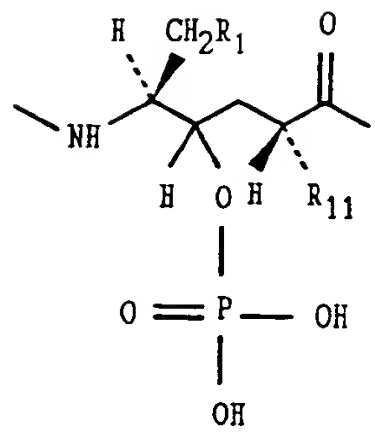
II



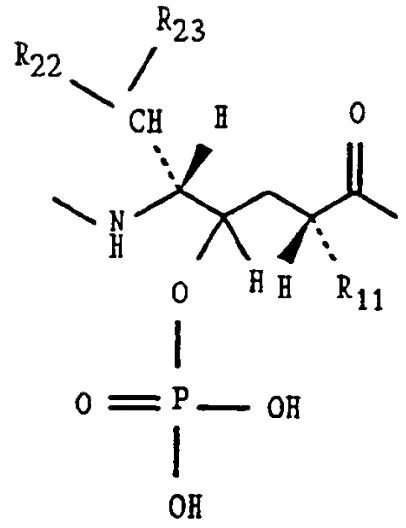
III



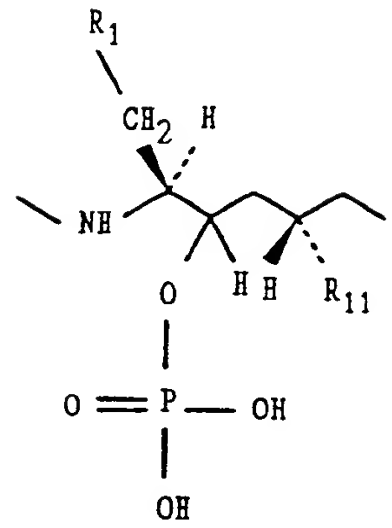
IV



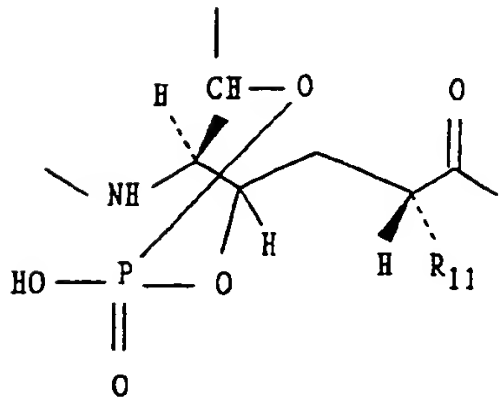
$XL_{6p}$'



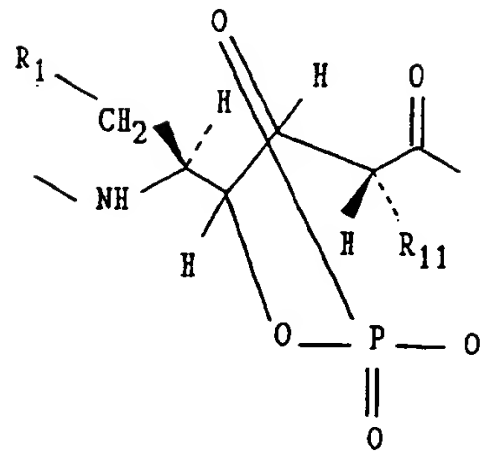
$XL_{6cp}$'



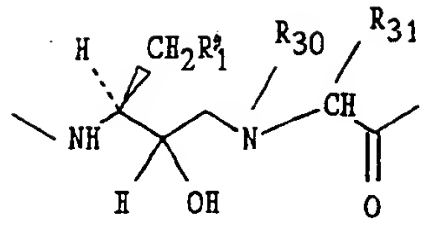
$XL_{6ep}$'



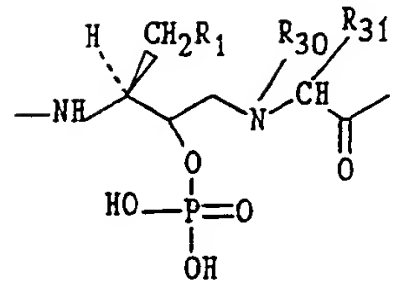
$XL_{6ccp}$'



$II_{cp}$'



V



Vp

wherein the variables are as defined in claim 1.

3. The compound of claim 1

wherein $X_1$ is

a) 2-pyridinyl-carbonyl,

b) 3-pyridinyl-CH=CH-carbonyl,

c) 3-pyridinyl-$(CH_2)_2$-carbonyl,

d) (3-pyridinyl)methoxycarbonyl,

e) 2-[2-(2-(2-methoxy)ethoxy)ethoxy)ethoxy]benzoyl,

f) (2-pyridinyl)methoxycarbonyl, or

g) (4-pyridinyl)methoxycarbonyl;

wherein $C_8$ is absent;

wherein $D_9$ is absent;

wherein $E_{10}$-$F_{11}$ is 5-amino-6-cyclohexyl-4-(O-phosphoryl)-2-isopropylhexanoyl or CVP;

wherein $G_{12}$ is Ile or absent;

wherein Z is

a) 2-(aminomethyl)pyridine,

b) 2-(aminomethyl)benzimidazole, or

c) 1-amino-2-hydroxy-indane;

4. The compound of claim 3 wherein the compound is selected from the group consisting of:

$N_\alpha$-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-(O-phosphoryl)-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide, hydrochloric acid salt or 2-Pyridinylcarbonyl-$(OPO_3H_2)$CVA-Ile-Amp;

$N_\alpha$-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-(O-phosphoryl)-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide trifluoroacetic acid salt or 2-Pyridinylcarbonyl-$(OPO_3H_2)$CVA-Ile-Amp;

$N_\alpha$-[(2S,4S,5S)-5-[N-[2-(3-Pyridinyl)ethenylcarbonyl]amino]-6-cyclohexyl-4-(0-phosphoryl)-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide, hydrochloric acid salt or 3-Pyridinyl-CH=CH-C(O)-($OPO_3H_2$)CVA-Ile-Amp;

$N_\alpha$-[(2S,4S,5S)-5-[N-[2-(3-Pyridinyl)-ethylcarbonyl]amino]-6-cyclohexyl-4-(0-phosphoryl)-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide, hydrochloric acid salt or 3-Pyridinyl-$(CH_2)_2$-C(O)-($OPO_3H_2$)CVA-Ile-Amp;

Nα-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-(O-phosphoryl)-2-isopropyl-1-oxohexyl]-N-(2-benzimidazolylmethyl)-L-isoleucinamide, trifluoroacetic acid salt or 2Py CO CVP Ile Amb;

N-[(2S,4S,5S)-5-[N-[2-(3-Pyridinyl)ethenylcarbonyl]amino]-6-cyclohexyl-4-(O-phosphoryl)-2-isopropyl-1-oxohexyl]-N-[(1S,2R)-2-hydroxy-1-indanyl]amine or 3Py CH=CHCO CVP Ahi;

N-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-(O-phosphoryl)-2-isopropyl-1-oxohexyl]-N-[(1S,2R)-2-hydroxy-1-indanyl]amine, trifluoroacetic acid salt or 2Py CO CVP Ahi;

Nα-[(2S,4S,5S)-5-[N-[(3-Pyridinyl)methoxycarbonyl]amino]-6-cyclohexyl-4-(O-phosphoryl)-2-isopropyl-1-oxohexyl]-N-(2-benzimidazolylmethyl)-L-isoleucinamide, trifluoroacetic acid salt or 3Poc CVP Ile Amb; and

Nα-[(2S,4S,5S)-5-[N-[2-[2-[2-(2-Methoxyethoxy)ethoxy]ethoxy]phenylcarbonyl] amino]-6-cyclohexyl-4-(O-phosphoryl)-2-isopropyl-1-oxohexyl]-N-(2-benzimidazolylmethyl)-L-isoleucinamide or Mee CVP Ile Amb.

5. The compound of claim 1

wherein $X_1$ is

a) naphthyloxyacetyl,

b) des-amino-tyrosine ($OPO_3H_2$), or

c) ((5-(3,6,9,12,15-pentaoxa-hexadec-1-yl)oxy)naphthalen-1-yl)oxyacetyl;

wherein $C_8$ is absent;

wherein $D_9$ is

a) His,

b) O-phosphoryl-threonyl,

c) O-phosphoryl-seryl,

d) Thr, or

e) Val;

wherein $E_{10}$-$F_{11}$ is:

a) 5-amino-6-cyclohexyl-3, 4-O, O-hydroxyphosphoryl-2-isopropyl-hexanoyl,

b) 5-amino-6-cyclohexyl-4-hydroxy-2-isopropyl-hexanoyl or CVA,

c) 5-amino-6-cyclohexyl-3, 4-dihydroxy-2-isopropyl-hexanoyl or CVD, or

d) 5-amino-6-cyclohexyl-4-(O-phosphoryl)-2-isopropylhexanoyl or $(OPO_3H_2)$CVA;

wherein $G_{12}$ is:

a) Ile,

b) O-phosphoryl-seryl, or

c) absent;

wherein Z is:

a) 2-(aminomethyl)pyridine,

b) 1-amino-2-hydroxy-indane, or

c) 2-(aminomethyl)-benzimidazole;

6. The compound of claim 5 wherein the compound is selected from the group consisting of:

1-Naphthoxyacetyl-L-histidyl-5S-amino-6-cyclohexyl-3R,4R-O,O-hydroxyphosphoryl-2R-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide;

1-Naphthoxyacetyl-L-histidyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-O-phosphoryl-L-seryl-2-pyridylmethylamide;

Noa-O-$PO_3K_2$-Thr-CVA-Ile-Amp; or 1-naphthoxyacetyl-O-phosphoryl-L-threonyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine, dipotassium salt;

Noa-O-$PO_3K_2$-Ser-CVA-Ile-Amp; or 1-naphthoxyacetyl-O-phosphoryl-L-seryl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine, dipotassium salt;

Dat(O-$PO_3H_2$)-His-CVA-Ile-Amp or 3-(O-phosphoryl-4-OH-phenyl)-butyryl-L-histidyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine;

$N_\alpha$-[(2S,4S,5S)-5-[N-[$N_\alpha$-(1-Naphthalenyloxy acetyl)-L-histidyl]amino]-6-cyclohexyl-4-(O-phosphoryl)-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide, trifluoroacetic acid salt or NOA-His-$(OPO_3H_2)$CVA-Ile-Amp;

((5-(3,6,9,12,15-pentaoxa-hexdec-1-yl)oxy)naphthalen-1-yl)oxyacetyl-O-phosphoryl-L-threonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine, dipotassium salt; or 5-PentaegNoa-$OPO_3K_2$-Thr-CVD-Ile-Amp;

((5-(3,6,9,12,15-pentaoxa-hexdec-1-yl)oxy)naphthalen-1-yl)oxyacetyl-O-phosphoryl-L-threonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-

aminomethylbenzimidazole, dipotassium salt; or 5-PentaegNoa-$OPO_3K_2$-Thr-CVD-Ile-Amb;

((5-(3,6,9,12,15-pentaoxa-hexdec-1-yl)oxy)naphthalen-1-yl)oxyacetyl-O-phosphoryl-L-threonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-1S-amino-2R-hydroxy-indane, dipotassium salt; or 5-PentaegNoa-$OPO_3K_2$-Thr-CVD-Ahi;

(1-naphthoxy)acetyl-O-phosphoryl-L-threonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine, dipotassium salt; or Noa-$OPO_3K_2$-Thr-CVD-Ile-Amp;

(1-naphthoxy)acetyl-O-phosphoryl-L-threonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole, dipotassium salt; or Noa-$OPO_3K_2$-Thr-CVD-Ile-Amb; and

(1-naphthoxy)acetyl-O-phosphoryl-L-threonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-1S-amino-2R-hydroxy-indane, dipotassium salt; or Noa-$OPO_3K_2$-Thr-CVD-Ahi.

7. A compound selected from the group consisting of:

Nα-[(2S, 4S, 5S)-5-[N-(3-Indolymethylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide; or 3-Indolyl-$CH_2$-C(O)-CVA-Ile-Amp;

Nα-[(2S, 4S, 5S)-5-[N-(2-Indolycarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide; or 2-Indolyl-C(O)-CVA-Ile-Amp;

Nα-[(2S, 4S, 5S)-5-[N-[[2-(3-Indoly)ethyl]carbonyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide; or 3-Indolyl-$(CH_2)_2$-C(O)-CVA-Ile-Amp;

Nα-[(2S, 4S, 5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide; or 2-Pyridinyl-C(O)-CVA-Ile-Amp;

Nα-[(2S, 4S, 5S)-5-[N-(3-Pyridinylmethylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide; or 3-Pyridinyl-$CH_2$C(O)-CVA-Ile-Amp;

Nα-[(2S, 4S, 5S)-5-[N-[(S)-Acetoxybenzylmethylcarbonyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide; or (S)-O-Acetyl-3-phenyllactyl-CVA-Ile-Amp;

Nα-[(2S, 4S, 5S)-5-[N-(2-(3-Pyridinyl)ethenylcarbonyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide; or 3-Pyridinyl-CH=CHC(O)-CVA-Ile-Amp;

Nα-[(2S, 4S, 5S)-5-[N-[2-(3-Pyridinyl)ethylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide; or 3-Pyridinyl-$(CH_2)_2$-C(O)-CVA-Ile-Amp;

Nα-[(2S, 4S, 5S)-5-[N-(4-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide; or 4-Pyridinyl-C(O)-CVA-Ile-Amp;

Nα-[(2S, 4S, 5S)-5-[N-(4-Quinolinylcarbonyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide; or 4-Quinolinyl-C(O)-CVA-Ile-Amp;

Nα-[(2S, 4S, 5S)-5-[N-(3-Quinolinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide; or 3-Quinolinyl-C(O)-CVA-Ile-Amp;

Nα-[(2S, 4S, 5S)-5-[N-(3-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide; or 3-Pyridinyl-C(O)-CVA-Ile-Amp;

Nα-[(2S, 4S, 5S)-5-[N-(2-Pyrrolylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide; or 2-Pyrrolyl-C(O)-CVA-Ile-Amp;

Nα-[(2S, 4S, 5S)-5-[N-(γ-L-Glutamyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide, trifluoroacetic acid salt; or γ-Glutamyl-CVA-Ile-Amp;

Nα-[(2S, 4S, 5S)-5-[N-(Succinoyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide, trifluoroacetic acid salt; or $HO_2C(CH_2)_2$-C(O)-CVA-Ile-Amp;

Nα-[(2S, 4S, 5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-(2, 4-diamino-6-pyrimidinylamino)ethyl]-L-isoleucinamide; or 2-Pyridinyl-C(O)-CVA-Ile-$NH(CH_2)_2$-NH-2,4-diamino-6-pyrimidinyl;

Nα-[(2S, 4S, 5S)-5-[N-(γ-L-Glutaryl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-pyridinylmethyl)-L-isoleucinamide, trifluoroacetic acid salt; or $HO_2C(CH_2)_3$-C(O)-CVA-Ile-Amp;

Nα-[(2S, 4S, 5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-[2-(2-pyridinylamino)ethyl)-L-isoleucinamide; or 2-Pyridinyl-C(O)-CVA-Ile-$NH(CH_2)_2$-NH-2-pyrinidinyl;

Hydroxyacetyl-5S-amino-6-cyclohexyl-3R, 4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or (HO)Ac-CVD-Ile-Amp;

L-Glycyl-5S-amino-6-cyclohexyl-3R, 4R-dihydroxy-2R-isopropyl-hexanoyl-L-

isoleucyl-2-pyridylmethylamide: or Gly-CVD-Ile-Amp;

Hydroxyacetyl-5S-amino-2R-benzyl-6-cyclohexyl-3R, 4R-dihydroxy-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or (HO) Ac-CPD-Ile-Amp;

Hydroxyacetyl-5S-amino-2R-benzyl-6-cyclohexyl-3R, 4R-dihydroxy-hexanoyl-L-isoleucyl-2-pyridylmethylamide N-oxide; or (HO) Ac-CPD-Ile-Amp-NO;

L-Glycyl-5S-amino-2R-benzyl-6-cyclohexyl-3R, 4R-dihydroxy-hexanoyl-L-isoleucyl-2-pyridylmethylamide: or Gly-CPD-Ile-Amp;

1-Adamantanecarbonyl-5S-amino-6-cyclohexyl-3R, 4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or 1-Adamantanecarbonyl-CVD-Ile-Amp;

Cyclohexanecarbonyl-5S-amino-6-cyclohexyl-3R, 4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or Cyclohexanecarbonyl-CVD-Ile-Amp;

3R-Quinuclidineaminocarbonyl-5S-amino-6-cyclohexyl-3R, 4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or 3R-Quinuclidineaminocarbonyl-CVD-Ile-Amp;

3S-Quinuclidineaminocarbonyl-5S-amino-6-cyclohexyl-3R, 4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or 3S-Quinuclidineaminocarbonyl-CVD-Ile-Amp;

N-(4-Quinolinyl)oxyacetyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or (4-Quinolinyl)oxyacetyl-CVA-Ile-Amp;

N-(5-Quinolinyl)oxyacetyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide; or (5-Quinolinyl)oxyacetyl-CVA-Ile-Amp;

Ac-CVA-Ile-8-aminoquinoline;

Hexanoyl-CVA-Ile-Amp;

Ac-CVA-Val-Amp;

Ac-CVA-Ile-aminomethyl-benzimidazole;

Nα-[(2S,4S,5S)-5-[N-[2-(3-Pyridinyl)ethenylcarbonyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-[2-(2-pyridinylamino)ethyl]-L-isoleucinamide; or 3Py CH=CHCO CVA Ile $NH(CH_2)_2NH$ 2Py;

Nα-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-benzimidazolylmethyl)-L-isoleucinamide; or 2Py CO CVA Ile Amb;

Nα-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-[(2-hydroxy-2-phenyl)ethyl]-L-isoleucinamide; or 2Py CO CVA Ile Hpa;

Nα-[(2S,4S,5S)-5-[N-[2-(3-Pyridinyl)ethenylcarbonyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-benzimidazolylmethyl)-L-isoleucinamide; or 3Py

CH=CHCO CVA Ile Amb;

Nα-[(2S,4S,5S)-5-[N-[(3-Pyridinyl)methoxycarbonyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-benzimidazolylmethyl)-L-isoleucinamide; or 3Poc CVA Ile Amb;

N-[(2S,4S,5S)-5-[N-[2-(3-Pyridinyl)ethenylcarbonyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-[(1S,2R)-2-hydroxy-1-indanyl]amine; or 3Py CH=CHCO CVA Ahi;

Nα-[(2S,4S,5S)-5-[N-[(4-Pyridinyl)methoxycarbonyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-benzimidazolylmethyl)-L-isoleucinamide; or 4Poc CVA Ile Amb;

Nα-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-[4-[(3-nitro-2-pyridinyl)amino]-2-butenyl]-L-isoleucinamide; or 2Py CO CVA Ile Npb;

Nα-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-[4-[(3-amino-2-pyridinyl)amino]-2-butenyl]-L-isoleucinamide; or 2Py CO CVA Ile Apb;

Nα-[(2S,4S,5S)-5-[N-[(2-Pyridinyl)methoxycarbonyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-benzimidazolylmethyl)-L-isoleucinamide; or 2Poc CVA Ile Amb;

Nα-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-[2-[(3-nitro-2-pyridinyl)amino]ethyl]-L-isoleucinamide; or 2Py CO CVA Ile Npe;

Nα-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-[2-[(3-amino-2-pyridinyl)amino]ethyl]-L-isoleucinamide; or 2Py CO CVA Ile Ape;

N-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-[(1S,2R)-2-acetoxy-1-indanyl]amine; or 2Py CO CVA Aai;

N-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-[(1S,2R)-2-hydroxy-1-indanyl]amine; or 2Py CO CVA Ahi;

N-[(2S,4S,5S)-5-[N-(2-Pyridinylcarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-[4-[(3-nitro-2-pyridinyl)amino]-2-butenyl]amine; or 2Py CO CVA Npb;

N-[(2S,4S,5S)-5-[N-[(3-Pyridinyl)methyoxycarbonyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-[(1S,2R)-2-hydroxy-1-indanyl]amine; or 3Poc CVA Ahi;

N-[(2S,4S,5S)-5-[N-[(2-Pyridinyl)methoxycarbonyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-[(1S,2R)-2-hydroxy-1-indanyl]amine; or 2Poc CVA Ahi;

*tert*-butyloxycarbonyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-threonyl-2-aminomethylpyridine; or Boc-CVA-Thr-Amp;

*tert*-butyloxycarbonyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-seryl-2-aminomethylpyridine; or Boc-CVA-Ser-Amp;

2-acetoxybenzoyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Acb-CVA-Ile-Amp;

2-hydroxybenzoyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Hyb-CVA-Ile-Amp;

2-[(2-phenoxy)ethoxy]benzoyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Peb-CVD-Ile-Amp;

Nα[(2S,4S,5S)-5-[N-[2-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]phenyl-carbonyl]amino]-6-cyclohexyl-4-hydroxy-2-isopropyl-1-oxohexyl]-N-(2-benzimidazolylmethyl)-L-isoleucinamide or Mee CVA Ile Amb;

2-[(2-phenoxy)ethoxy]benzoyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Peb-CVD-Ile-Amb;

2-[(2-phenoxy)ethoxy]benzoyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-*tert*-butylmethylamine; or Peb-CVD-Ile-Tma;

2-[(2-phenoxy)ethoxy]benzoyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-2-aminomethylbenzimidazole; or Peb-CVD-Amb;

4-methyl-2-[(2-phenoxy)ethoxy]benzoyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Mpb-CVD-Ile-Amb;

2-[(phenylthio)methoxy]benzoyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Ptb-CVD-Ile-Amb;

3-[(2-phenoxy)ethoxy]propionyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Pep-CVD-Ile-Amb;

2-[2-(2-(2-methoxy)ethoxy)ethoxy)ethoxy]benzoyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Mee-CVD-Ile-Amb;

2-[(2-methoxy)ethoxy]benzoyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Meb-CVD-Ile-Amb;

2-[2-(2-methoxy)ethoxy)ethoxy]benzoyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Mtb-CVD-Ile-Amb;

2-[(2-phenoxy)ethoxy]benzoyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Peb-CVA-Ile-Amb;

hydroxyacetyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Hydroxyacetyl-CVA-Ile-Amb;

2-hydroxy-3-methylbutryl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Hmb-CVA-Ile-Amb (less polar isomer);

2-hydroxy-3-methylbutryl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Hmb-CVA-Ile-Amb (more polar isomer);

3-(4-hydroxyphenyl)-butyryl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Dat-CVA-Ile-Amp;

4-hydroxyphenylacetyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or 4-Hpa-CVA-Ile-Amb;

2-hydroxyphenylacetyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or 2-Hpa-CVA-Ile-Amb;

3-hydroxyphenylacetyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or 3-Hpa-CVA-Ile-Amb;

3-(4-hydroxyphenyl)-butyryl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Dat-CVA-Ile-Amb;

3-(4-hydroxyphenyl)-butyryl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-1S-amino-2R-hydroxy-indane; or Dat-CVD-Ahi;

2-((3-(4-(3,6,9-trioxadec-1-yloxy)phenyl)prop-1-yl)oxy)benzoyl-5*S*amino-6-cyclohexyl-3*R*,4*R*-dihydroxy-2*R*-isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine;

2-[(2-phenoxy)ethoxy]benzoyl-5*S*-amino-6-cyclohexyl-3*R*,4*R*-dihydroxy2*R*-isopropyl-hexanoyl-L-isoleucinyl-1-aminoethyl(4-methylthiazole);

2-(2-(4-methylthiazol-5-yl)ethyl)oxy)benzoyl-5*S*-amino-6-cyclohexyl3*R*,4*R*-dihydroxy-2*R*-isopropyl-hexanoyl-L-isoleucinyl-2aminomethylpyridine;

2-(2-(4-methylthiazol-5-yl)ethyl)thio)benzoyl-5*S*-amino-6cyclohexyl-3*R*,4*R*-dihydroxy-2*R*-isopropyl-hexanoyl-L-isoleucinyl-2aminomethylpyridine;

2-(2-(4-methylthiazol-5-yl)ethyl)oxy)benzoyl-5*S*-amino-6-cyclohexyl3*R*,4*R*-dihydroxy-2*R*-isopropyl-hexanoyl-L-isoleucinyl-1-aminoethyl(4methylthiazole);

2-(2-(4-methylthiazol-5-yl)ethyl)thio)benzoyl-5*S*-amino-6cyclohexyl-3*R*,4*R*-dihydroxy-2*R*-isopropyl-hexanoyl-L-isoleucinyl 1aminoethyl(4-methylthiazole);

2-((4-([3a*S*-(3a$\alpha$,4$\beta$,6a$\alpha$)]-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-on-4yl)pent-1-yl)thio)benzoyl-5*S*-amino-6-cyclohexyl-3*R*,4*R*-dihydroxy-2*R*isopropyl-hexanoyl-L-isoleucinyl-amino-2-(4-methylthiazol-5yl)ethane;

2-((4-([3a*S*-(3a$\alpha$,4$\beta$,6a$\alpha$)]-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-on-4yl)pent-1-yl)oxy)benzoyl-5*S*-amino-6-cyclohexyl-3*R*,4*R*-dihydroxy-2*R*isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine;

4-([3a*S*-((3a$\alpha$,4$\beta$,6a$\alpha$)]-1*H*-thieno[3,4-*d*]imidazolyl)pentanoyl-5*S*amino-6-cyclohexyl-3*R*,4*R*-dihydroxy-2*R*-isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine; or Biotinoyl-CVD-Ile-AMP;

4-([3a*S*-(3a$\alpha$,4$\beta$,6a$\alpha$)]-1*H*-thieno[3,4-*d*]imidazolyl)pentanoyl-6aminohexanoyl-5*S*-amino-6-cyclohexyl-3*R*,4*R*-dihydroxy-2*R*-isopropylhexanoyl-L-isoleucinyl-2-

aminomethylpyridine; or Biotinoyl-Aminohexanoyl-CVD-Ile-AMP;

2-[(2-phenoxy)ethoxy]benzoyl-5*S*-amino-2*S*-benzyl-3*R*,4*R*-dihydroxy-7methyl-octanoyl-L-isoleucinyl-2-aminomethylpyridine; or Pep-LFD-Ile-Amp;

2-[(2-phenoxy)ethoxy]benzoyl-5*S*-amino-2*S*-benzyl-3*R*,4*R*-dihydroxy-7methyl-octanoyl-L-isoleucinyl-amino-2-(4-methylthiazol-5-yl)ethane;

2-[(2-phenoxy)ethoxy]benzoyl-5*S*-amino-2*S*-benzyl-3*R*,4*R*-dihydroxy-7methyl-octanoyl-L-isoleucinyl-2-aminomethylbenzimidazole; or Pep-LFD-Ile-Amb; and

2-((3-(4-(3,6,9-trioxadec-1-yloxy)phenyl)prop-1-yl)oxy)benzoyl-5*S*amino-2*S*-benzyl-3*R*,4*R*-dihydroxy-7-methyl-octanoyl-1*S*-amino-2*R*hydroxy-indane.

8. A compound selected from the group consisting of:

1-naphthoxyacetyl-L-histidyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-threonyl-2-aminomethylpyridine; or Noa-His-CVA-Thr-Amp;

1-naphthoxyacetyl-L-valyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-seryl-2-aminomethylpyridine; or Noa-Val-CVA-Ser-Amp;

1-naphthoxyacetyl-L-valyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-threonyl-2-aminomethylpyridine; or Noa-Val-CVA-Thr-Amp;

1-naphthoxyacetyl-L-threonyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Noa-Thr-CVA-Ile-Amp;

1-naphthoxyacetyl-L-seryl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Noa-Ser-CVA-Ile-Amp;

methoxycarbonyl-D-prolyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Moc-D-Pro-CVA-Ile-Amp;

*tert*-butyloxycarbonyl-L-prolyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Boc-Pro-CVA-Ile-Amp;

methoxycarbonyl-L-prolyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Moc-Pro-CVA-Ile-Amp;

Acetyl-L-prolyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Ac-Pro-CVA-Ile-Amp;

1-naphthoxyacetyl-L-histidyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-1S-amino-2R-hydroxy-indane; or Noa-His-CVA-Ahi;

1-naphthoxyacetyl-L-histidyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-1S-amino-2R-hydroxy-indane; or Noa-His-CVD-Ahi;

1-naphthoxyacetyl-L-threonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Noa-Thr-CVD-Ile-Amb;

1-naphthoxyacetyl-L-seryl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-

hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Noa-Ser-CVD-Ile-Amb;

1-naphthoxyacetyl-L-homoseryl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Noa-Hsr-CVA-Ile-Amp;

1-naphthoxyacetyl-L-threonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-1S-amino-2R-hydroxy-indane; or Noa-Thr-CVD-Ahi;

1-naphthoxyacetyl-L-seryl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-1S-amino-2R-hydroxy-indane; or Noa-Ser-CVD-Ahi;

1-naphthoxyacetyl-L-histidyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-1S-amino-2R-hydroxy-indane; or Noa-His-CVD-Ahi;

4-morpholinecarbonyl-L-valyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Morph-Val-CVA-Ile-Amp;

acetyl-L-valyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Acetyl-Val-CVA-Ile-Amp;

1-naphthoxyacetyl-$N^{\alpha}$methyl-L-histidyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Noa-$N^{\alpha}$methyl-His-CVA-Ile-Amp;

3-(4-hydroxyphenyl)-butyryl-L-histidyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Dat-His-CVA-Ile-Amp;

5-OH-1-naphthoxyacetyl-L-histidyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or 5-OH-NOA-His-CVA-Ile-Amp;

3-(4-hydroxyphenyl)-butyryl-L-valyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or Dat-Val-CVA-Ile-Amb;

1-naphthylenyloxyacetyl-L-asparaginyl-5*S*-amino-6-cyclohexyl-4*S*hydroxy-2*S*-isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine; or Noa-Asn-CVA-Ile-Amp;

1-naphthalenyloxyacetyl-L-valinyl-5*S*-amino-6-cyclohexyl-4*S*-hydroxy2*S*-isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine; or Noa-Val-CVA-Ile-Amp;

((5-(3,6,9-trioxa-dec-1-yl)oxy)naphthalen-1-yl)oxyacetyl-L-asparaginyl-5*S*-amino-6-cyclohexyl-4*S*-hydroxy-2*S*-isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine; or 5-Trieg-Noa-His-CVA-Ile-Amp;

((5-(3,6,9-trioxa-dec-1-yl)oxy)naphthalen-1-yl)oxyacetyl-L-asparaginyl-5*S*-amino-6-cyclohexyl-4*S*-hydroxy-2*S*-isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine; or 4-Trieg-Noa-His-CVA-Ile-Amp;

((5-(3,6,9-trioxa-dec-1-yl)oxy)naphthal-1-yl)oxyacetyl-L-valinyl-5*S*amino-6-cyclohexyl-4*S*-hydroxy-2*S*-isopropyl-hexanoyl-L-isoleucinyl-2aminomethylpyridine; or 5-Trieg-Noa-Val-CVA-Ile-Amp;

((4-(3,6,9-trioxa-dec-1-yl)oxy)naphthalen-1-yl)oxyacetyl-L-valinyl5*S*-amino-6-

cyclohexyl-4*S*-hydroxy-2*S*-isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine; or 4-Trieg-Noa-Val-CVA-Ile-Amp;

((5-(8-amino-3,6-dioxa-oct-1-yl)oxy)naphthalen-1-yl)oxyacetyl-L-valinyl-5*S*-amino-6-cyclohexyl-3*R*,4*R*-dihydroxy-2*R*-isopropylhexanoyl-L-isoleucinyl-2-aminomethylpyridine;

((5-(8-trimethylamminyl-3,6-dioxa-oct-1-yl)oxy)naphthalen-1yl)oxyacetyl-L-valinyl-5*S*-amino-6-cyclohexyl-3*R*,4*R*-dihydroxy-2*R*isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine iodide;

naphthalene-2-sulfonyl-L-histidinyl-5*S*-amino-6-cyclohexyl-4*S*hydroxy-2*S*-isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine;

4-([3a*S*-(3a$\alpha$,4$\beta$,6a$\alpha$)]-1*H*-thieno[3,4-*d*]imidazolyl)pentanoyl-L-valinyl-5*S*-amino-6-cyclohexyl-3*R*,4*R*-dihydroxy-2*R*-isopropylhexanoyl-L-isoleucinyl-2-aminomethylpyridine; or Biotinoyl-Val-CVD-Ile-AMP;

naphthalene-2-sulfonyl-L-valinyl-5*S*-amino-2*S*-benzyl-3*R*,4*R*-dihydroxy7-methyl-octanoyl-L-isoleucinyl-2-aminomethylpyridine;

1-naphthyloxyacetyl-L-histidinyl-5*S*-amino-2*S*-benzyl-3*R*,4*R*-dihydroxy7-methyl-octanoyl-L-isoleucinyl-2-aminomethylpyridine; or Noa-His-LFD-Ile-Amp;

naphthalene-2-sulfonyl-L-asparaginyl-5*S*-amino-2*S*-benzyl-3*R*,4*R*dihydroxy-7-methyl-octanoyl-L-isoleucinyl-2-aminomethylpyridine;

naphthalene-2-sulfonyl-L-valinyl-5*S*-amino-2*S*-((2-phenyl)eth-1-yl)3*R*,4*R*-dihydroxy-7-methyl-octanoyl-L-isoleucinyl-2aminomethylpyridine;

naphthalene-2-sulfonyl-L-leucinyl-5*S*-amino-2*S*-benzyl-3*R*,4*R*dihydroxy-7-methyl-octanoyl-L-isoleucinyl-2-aminomethylpyridine; and

(1-naphthoxy)acetyl-L-threonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-iospropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or Noa-Thr-CVD-Ile-Amp.

9. A compound of the formula I

$$X_1\text{-}C_8\text{-}D_9\text{-}E_{10}\text{-}F_{11}\text{-}G_{12}\text{-}Z \qquad \text{I}$$

wherein $X_1$ is $X_2$-[$(CH_2)_2$-O]$_m$-aryl-O-$(CH_2)_n$-C(O)-;

wherein $X_2$ is

a) $H_3CO$-,

b) $(R_4)_2N$-, or

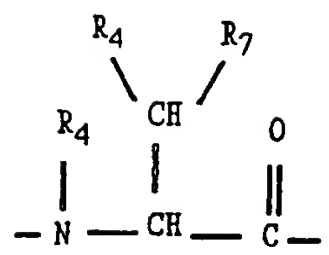
c) Het;

wherein m is five or six;

wherein n is zero to six, inclusive;

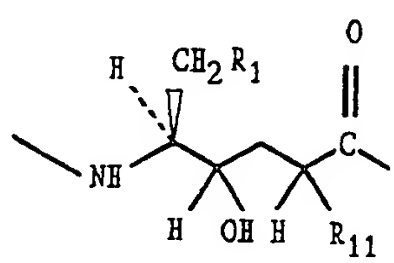
wherein $C_8$ is absent;

wherein $D_9$ is the moiety $XL_3$;

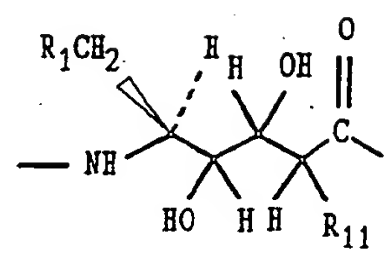


$XL_3$

wherein $E_{10}$-$F_{11}$ is the moiety $XL_6$ or II;

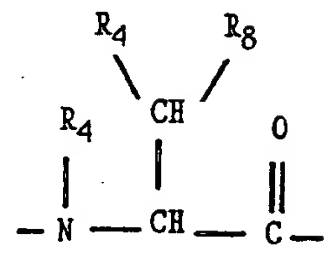


$XL_6$



II

wherein $G_{12}$ is absent or is the moiety $XL_4$;



$XL_4$

wherein Z is

a) $-N(R_4)_2$, or

b) $-NHX_3$;

wherein $X_3$ is

a) $-(CH_2)_n$-Het,

b) $-(CH_2)_n$-aryl, or

c) 1-amino indanyl optionally substituted at the 2- or 3- position by one or two hydroxy or $-OC(O)CH_3$;

wherein aryl is phenyl or naphthyl;

wherein -Het is a 5- or 6-membered saturated or unsaturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another heterocycle and the ring may be connected through a carbon or secondary nitrogen in

the ring or an exocyclic nitrogen;

wherein $R_1$ is

a) phenyl, ,

b) $C_3$-$C_7$ cycloalkyl, or

c) $C_1$-$C_5$ alkyl;

wherein $R_4$ is

a) hydrogen, or

b) $C_1$-$C_5$ alkyl;

wherein $R_7$ is

a) hydroxy,

b) Het, or

c) $C_1$-$C_5$ alkyl substituted by zero to three hydroxy;

wherein $R_8$ is

a) $C_1$-$C_5$ alkyl,

b) Het, or

c) aryl;

wherein $R_{11}$ is

a) -$(CH_2)_n$- phenyl,

b) -$(CH_2)_n$-$C_3$-$C_7$ cycloalkyl, or

c) $C_1$-$C_5$ alkyl;

and pharmacologically acceptable salts thereof.

10. The compound of claim 9 selected from the group consisting of:

((5-(3,6,9,12,15-pentaoxa-hexadec-1-yl)oxy)naphthalen-1yl)oxyacetyl-L-histidinyl-5*S*-amino-6-cyclohexyl-4*S*-hydroxy-2*S*isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine; or 5-Pentaeg-Noa-His-CVA-Ile-Amp;

((5-(3,6,9,12,15,18-hexaoxa-nonadec-1-yl)oxy)naphthalen-1yl)oxyacetyl-L-histidinyl-5*S*-amino-6-cyclohexyl-4*S*-hydroxy-2*S*isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine; or 5-Hexaeg-Noa-His-CVA-Ile-Amp;

((5-(3,6,9,12,15-pentaoxa-hexadec-1-yl)oxy)naphthalen-1yl)oxyacetyl-L-histidinyl-5*S*-amino-6-cyclohexyl-3*R*,4*R*-dihydroxy-2*R*isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine; or 5-Pentaeg-Noa-His-CVD-Ile-Amp;

((5-(3,6,9,12,15-pentaoxa-hexadec-1-yl)oxy)naphthalen-1yl)oxyacetyl-L-valinyl-5*S*-amino-6-cyclohexyl- 3*R*,4*R*-dihydroxy-2*R*isopropyl-hexanoyl-L-isoleucinyl-2-aminomethylpyridine; or 5-PentaegNoa-Val-CVD-Ile-Amp;

((5-(3,6,9,12,15-pentaoxa-hexadec-1-yl)oxy)naphthalen-1yl)oxyacetyl-L-valinyl-5*S*-

amino-6-cyclohexyl-3*R*,4*R*-dihydroxy-2*R*isopropyl-hexanoyl-L-isoleucinyl-1*S*-amino-2*R*-hydroxy-indane; or 5-PentaegNoa-Val-CVD-Ile-Ahi;

((5-(3,6,9,12,15-pentaoxa-hexdec-1-yl)oxy)naphthalen-1-yl)oxyacetyl-L-threonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylpyridine; or 5-PentaegNoa-Thr-CVD-Ile-Amp;

((5-(3,6,9,12,15-pentaoxa-hexdec-1-yl)oxy)naphthalen-1-yl)oxyacetyl-L-threonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-L-isoleucyl-2-aminomethylbenzimidazole; or 5-PentaegNoa-Thr-CVD-Ile-Amb; and

((5-(3,6,9,12,15-pentaoxa-hexdec-1-yl)oxy)naphthalen-1-yl)oxyacetyl-L-threonyl-5S-amino-6-cyclohexyl-3R,4R-dihydroxy-2R-isopropyl-hexanoyl-1S-amino-2R-hydroxy-indane; or 5-PentaegNoa-Thr-CVD-Ahi.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/02238

| I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6] | | |
|---|---|---|
| According to International Patent Classification (IPC) or to both National Classification and IPC | | |
| Int.Cl. 5 C07K5/02; | C07F9/09; | A61K37/64 |

| II. FIELDS SEARCHED | |
|---|---|
| Minimum Documentation Searched[7] | |
| Classification System | Classification Symbols |
| Int.Cl. 5 | C07K ; C07F ; A61K |
| Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8] | |
| | |

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

| Category ° | Citation of Document,[11] with indication, where appropriate, of the relevant passages[12] | Relevant to Claim No.[13] |
|---|---|---|
| A | TETRAHEDRON LETTERS<br>vol. 27, no. 21, 1986, OXFORD, ENGLAND<br>pages 2337 - 2340;<br>DELLARIA ET AL: 'The enantio- and diastereoselective synthesis of the first phospho-statine derivative'<br>* See page 1 *<br>--- | 1-10 |
| A | RECUEIL DES TRAVAUX CHIMIQUES DE PAYS-BAS<br>vol. 109, no. 1, 1990, THE HAGUE, HOLLAND<br>pages 27 - 28;<br>DE BONT ET AL: 'N,N-diisopropyl-bis(4-chlorobenzyl)phosphoramidite: A versatile phosphitylating agent for the phosphorylation of hydroxy amino acids and preparation of protected phosphopeptides'<br>* See the whole document *<br>---<br>-/-- | 1-10 |

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 17 JULY 1992 | [illegible] |
| **International Searching Authority** | **Signature of Authorized Officer** |
| EUROPEAN PATENT OFFICE | KORSNER S.E. |

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

| Category ° | Citation of Document, with indication, where appropriate, of the relevant passages | Relevant to Claim No. |
|---|---|---|
| A | JOURNAL OF BIOCHEMISTRY<br>vol. 107, 1990, TOKYO, JAPAN<br>pages 68 - 72;<br>MEGA ET AL.: 'Modifications of substituted seryl and threonyl residues in phosphopeptides and a polysialoglycoprotein by Beta-elimination and nuclophile additions'<br>* See page 70, table 1 * | 1-10 |
| A | JOURNAL OF THE AMERICAN CHEMICAL SOCIETY<br>vol. 106, 1984, WASHINGTON, USA<br>pages 4282 - 4283;<br>BARTLETT ET AL: 'Phosphinic acid dipeptide analogues: Potent, slow-binding inhibitors of aspartic peptidases'<br>* See page 4282, col. 1 * | 1-10 |
| A | JOURNAL OF MEDICINAL CHEMISTRY<br>vol. 28, no. 11, 1985, WASHINGTON<br>pages 1553 - 1555;<br>THAISRIVONGS ET AL: 'Difluorostatine- and difluorostatone-containing peptides as potent an dspecific renin inhibitors'<br>* See page 1554, table 1 * | 1-10 |